Detail of Full Cost

The FY 2006 NIH budget request provides funding to support each of the core NIH programs. The following table provides a 3-year summary of funding (in millions) for NIH.[1]

Summary of Full Cost *
NATIONAL INSTITUTES OF HEALTH
(Dollars in Millions)

Performance Program Area		FY 2005	
NIH Budget Authority	$28,036	$28,594	$28,740
NIH Full Cost Research Program	28,036	28,594	28,740
SRO High Risk 1-3 Years	*6*	*6*	*2*
SRO High Risk 4-6 years	*33*	*36*	*32*
SRO High Risk 7-10 years	*1,516*	*1,596*	*1,711*
SRO Meidum Risk 1-3 Years	*95*	*9*	*0*
SRO Medium Risk 4-6 years	*835*	*829*	*798*
SRO Medium Risk 7-10 years	*98*	*72*	*82*
SRO Low Risk 1-3 Years	*30*	*13*	*12*
SRO Low Risk 4-6 years	*400*	*313*	*334*
SRO Low Risk 7-10 years	*107*	*107*	*84*
Communication and Transfer of Results	*4*	*4*	*4*
Capacity Building and Research Resources	*1,543*	*1,604*	*1,635*
Strategic Management of Human Capital	*4*	*14*	*6*
Program Oversight and Improvement	*1*	*1*	*1*
Full Cost Total	28,036	28,594	28,740

* Full cost data for the measures under each performance program area are shown as non-adds. The sum of full costs of performance measures does not equal the full cost of the performance program area, as NIH utilizes a representative sampling approach to report on program performance progress. Representative goals serve as proxies for performance of the larger research portfolio for each of the functional areas.

Methodology for Full Cost

NIH does not have an account or collection of accounts dedicated to program management. To allocate costs for program management, we selected the Research Management and Support (RMS) line item from the NIH mechanism display and Office of the Director Operations, a line item in the appropriation for the Office of the Director. Although these lines support some activities in addition to program management, they represent the majority of NIH program management activities. These totals were reduced by the direct costs of the performance goals that are funded through RMS or OD operations. This calculated level for Program Management was allocated across GPRA goals and the unsampled program on a pro-rata basis. The funding amounts devoted to each goal are included in the Program Performance Tables on pgs. NIH-96-122.

Budget and Performance Crosswalk

The FY 2005 Appropriation and the FY 2006 Estimate are detailed by budget mechanism in the NIH Overview to the FY2006 President's Budget. The NIH Budget Mechanism table for FY 2004 is provided below.

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

NIH BUDGET MECHANISM	FY 2004 ENACTED (COMPARABLE)[1] (DOLLARS IN MILLIONS)
Research Project Grants	$15,169
Research Centers	2,541
Other Research	1,601
Research Training	745
Research and Development Contracts	2,824
Intramural Research	2,653
Research Management and Support	1,033
Cancer Prevention and Control	530
Construction	119
Library of Medicine	308
Office of the Director	327
Buildings and Facilities	107
VA/HUD Superfund	78
All Mechanisms	$28,036

May not add due to rounding

BUDGET-GPRA INTEGRATION

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

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

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

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

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

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

DETAIL OF PERFORMANCE ANALYSIS

Program Performance Tables

Comprehensive summary tables covering all the FY 2004, 2005, and 2006 goals and targets in NIH's Research Program follow. These tables provide updated information on the status of all of the program's performance targets, as well as budget and performance integration. Due to the complexities of scientific discovery, the identified targets are subject to change. More extensive information on each goal, including a chart summarizing the performance results for each target, can be found in the Detailed GPRA Goal Performance Narratives by Functional Areas section. Healthy People 2010, PMA, HHS Strategic Plan, outcome, output, efficiency, and PARTed goals are noted in the reference column of the chart where appropriate.

Program Performance Tables: FY 2004, 2005, 2006 Performance Goals - dollars in millions

- **SCIENTIFIC RESEARCH OUTCOMES**

	By 2005, conduct medications development using animal models and begin conducting Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin.	**REFERENCE[1]**
		SP-1.4, 4.1, HP-26, Outcome, Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Prepare clinical protocol for testing rimonabant in humans.	1. Two drugs have been approved for use in the US to treat alcohol addiction, with limited effectiveness	1. (MET) Rimonabant has been shown to reduce ethanol intake in rodent models of voluntary ethanol drinking.
FY 2004 1. Complete a toxicologic evaluation on antalarmin.	1. Antalarmin and rimonabant show promise in nonhuman animal models as excellent candidates for Phase I clinical trials	1. (MET) A toxicologic evaluation on antalarmin has been completed.
FY 2005 1. Test antalarmin for relapse prevention in alcoholics.	1. Recent studies have shown that antalarmin reduces voluntary ethanol intake in rat model of drinking	1. Performance results will be reported in February 2006.

aKU-1.2	By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.	REFERENCE[1]: SP-4.1, 6.2, HP-28, Outcome, PART

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Design and test a device (diaphragm) that responds to sound based on the ears of the parasitic fly *Ormia ochracea.*	1. Small insect model system exists and has hyperacute sound localization	1. (MET) NIH scientists successfully completed design and testing of a novel microphone diaphragm that responds to sound and is based on the ears of the parasitic fly *Ormia ochraca.*
***FY* 2004** 1. Design and test the electronic circuitry to create a sound output from the diaphragm.	1. Sound-responsive diaphragm based on an insect model system is available	1. (MET) NIH-supported scientists successfully developed the electronic output circuitry that will convert the microphone diaphragm's motion into an electronic signal.
FY 2005 1. Combine the diaphragm and the electronic output circuitry into a directional microphone that is small enough to fit into a hearing aid. ***Adjusted to:*** Combine the diaphragm and the electronic output circuitry into a directional microphone.	1. Diaphragm and electronic circuitry are available	1. Performance results will be reported in February 2006.
FY 2006 1. Develop a fabrication process to miniaturize the prototype directional microphone so that it will fit into a hearing aid.	1. Prototype directional microphone is available	1. Performance results will be reported in February 2007.

FULL COST (dollars in millions)	FY 04	FY 05	FY 06
	$6	$6	$2

SRO-2.2	By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.	REFERENCE[1]: SP-U, HP-19, Outcome, Efficiency

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Identify two new drug targets that can be used in screens for potentially therapeutic compounds in drug discovery projects or that could be evaluated for use as therapeutic agents for weight control.	1. No highly effective drug therapies exist for overweight or obesity. Potential drug targets need to be identified	1. (MET) Three molecules can be characterized and screened as targets for therapeutic compounds or evaluated as potential therapeutic agents for weight control.
FY 2004 1. Develop and launch at least two studies to test the effects of worksite interventions on weight control.	1. No programs for weight control at the worksite have been examined in studies with valid designs to clearly evaluate if they are effective	1. (MET) More than two studies to test the effects of worksite interventions on weight control were developed and launched.
FY 2005 1. Enroll and randomize 60 children with hyperinsulinimia in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children ages 6 to 12 years.	1. No clinical trials have demonstrated efficacy of any medication for overweight during childhood. Pilot data suggest metformin may be of benefit for those children with hyperinsulinemia	1. Performance results will be reported in February 2006.
FY 2006 1. Enroll and randomize 240 predominantly minority pre-adolescent girls to test the efficacy of an after school dance program in reducing weight gain.	1. Few effective community-based interventions are available to prevent weight gain in at risk children	1. Performance results will be reported in February 2007.

		REFERENCE'
1 SRO-2.3 1	**By 2006, develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.**	

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Develop software for making comparative alignments of protein domains according to structure and molecular evolutionary classification, and which provides functions for domain family updates.	1. 256 domain families curated; software to align domains by structure and class unavailable	1. (MET) Software was released which improved structure-based alignments of proteins and classification of protein domain families based on molecular evolution; software was used to annotate over 500 protein domain families.
FY 2004 1. Obtain annotation for a total of 1,500 protein domain families in the conserved domain database using two advanced classification methods: (1) structure-based alignment and (2) molecular evolutionary classification. Cover 35% of sequences in PubMed (the National Library of Medicine's database of biomedical research literature), extended to 70% by adding first-generation alignments.	1. 800 domain families curated; 25% coverage of PubMed sequences	1. (MET) 1,674 domain families curated through enhancing software for molecular evolutionary classification and by bringing Conserved Domain Curator team to full strength.
FY 2005 1. Obtain annotation for a total of 2,500 protein domain families annotated by structure-based alignment and molecular evolutionary classification. Cover 45% of PubMed sequences, extended to 75% by adding first-generation alignments.	1. 1,500 protein domain families curated; 35% coverage of PubMed sequences	1. Performance results will be reported in February 2006.
FY 2006 1. Obtain annotation for total of 3,500 protein domain families annotated by structure-based alignment and molecular evolutionary classification. Cover 55% of PubMed sequences.	1. 2,500 protein domain families curated; 45% coverage of PubMed sequences	1. Performance results will be reported in February 2007.

FULL COST (dollars in millions)	FY 04	FY 05	FY 06
	$33	$36	$32

1 SRO 3 1 1 1 SRO-3.1 1	**By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease.**	REFERENCE'
		SP-4.1, 6.2, HP-18, Outcome, PART

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Initiate a double blind, placebo-controlled trial of simvastatin (medication used to reduce the amount of cholesterol and certain fatty substances in the blood) to determine whether it can slow the rate of progression of AD.	1. Earlier studies indicate lowering cholesterol levels with statins seems to have a positive impact on brain function and reduces the risk of AD	1. (MET) CLASP study was enacted to further investigate the role that cholesterol has in the pathogenesis of Alzheimer's Disease.
FY 2004 1. Identify and implement effective strategies to facilitate drug discovery and development for AD treatment and prevention in collaboration with relevant organizations, as well as through stimulation of relevant research through Program Announcements and/or other mechanisms.	1. Estimated 30 compounds are presently or will soon be tested in human AD clinical trials but additional targets are needed	1. (MET) NIH initiated a preclinical toxicology program and expanded an interventions testing program to expedite drug discovery, and identified a collaborative opportunity for pre-clinical drug development.
FY 2005 1. Launch the Alzheimer's Disease Neuroimaging Initiative to evaluate neuroimaging modalities and techniques and other biomarkers to be used in early diagnosis, follow the progression of mild cognitive impairment and AD, and use as potential surrogate markers for drug development and clinical trials.	1. Neuroimaging technologies appear to have considerable potential for early diagnosis of MCI and AD and for measuring disease progression	1. Performance results will be reported in February 2006.
FY 2006 1. Identify around 1,000 new late onset AD families to allow geneticists to locate additional late onset	1. The genetics initiative has identified 259 families, too few	1. Performance results will be reported in February 2007.

risk factor genes for AD that may lead to new targets for drug treatment, and provide a well-characterized population for more efficient clinical trials.	for researchers to identify the remaining risk factor genes	

	By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.	**REFERENCE**[1]
		SP-2.1, 4.1, HP-14, 24, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Identify one molecule with a common role in bacterial and viral infections that may serve as a target for broad-spectrum antimicrobial drug development.	1. None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule with a common role in both bacteria and viruses	1. (MET) Two different molecules with a common role in different classes of microbes were identified.
FY 2004 1. Identify one molecule or mechanism that is shared by a class or across different classes of microbes that may serve as a target for broad-spectrum antimicrobial drug development.	1. None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes	1. (MET) A drug/metabolite transporter molecule from the malarial parasite *Plasmodium falciparum,* that is similar to transporter molecules in other protozoa, may serve as a target for drugs to increase responsiveness to drug therapies.
FY 2005 1. Develop a lead compound for one of the molecules or mechanisms identified as a potential target for broad-spectrum antimicrobial drug development. ***Adjusted to:*** Develop a set of screening tools that will help evaluate potential compounds/classes of compounds for activity against multiple bacterial and viral infections.	1. None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes	1. Performance results will be reported in February 2006.
FY 2006 1. Use screening tools to evaluate potential compounds or classes of compounds for activity against multiple classes of infectious diseases.	1. Screening tools for evaluation of potential compounds/classes of compounds for activity against multiple bacterial and viral infections developed	1. Performance results will be reported in February 2007.

	By 2013, determine the efficacy of using salivary diagnostics to monitor	**REFERENCE**[1]
	health and diagnose at least one systemic disease.[2]	SP—4.1, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Implement at least five research projects directed at developing integrated technologies for the efficient and simultaneous detection of key molecules in human saliva.	1. No integrated technologies to quickly and efficiently measure multiple substances in saliva	1. (MET) Seven research projects implemented to develop technology aimed at human salivary diagnostics.
FY 2004 1. Implement research projects directed at identifying and cataloging saliva proteomes. Identification of salivary proteomes will help scientists detect changes in saliva that are associated with specific diseases or conditions.	1. Technology available to help identify salivary proteomes	1. (MET) Three research projects implemented to identify and catalog salivary proteomes.
FY 2005 1. Develop electronic microfluidic assay systems (e.g., microchip-based systems that are replacing large and costly instruments) that can quantify C-reactive protein (a biomarker for cardiovascular disease) in saliva.	1. Systems to quantify C-reactive protein in saliva have not yet been developed	1. Performance results will be reported in February 2006.
FY 2006 1. Finalize the fabrication of a portable handheld diagnostic device that can detect C-reactive protein and other analytes associated with oral and/or systemic diseases, and develop methods for its quality assurance and standardization.	1. Currently the individual components needed for a portable handheld diagnostic device are under fabrication and validation	1. Performance results will be reported in February 2007.

SRO-3.4 By 2010, develop an HIV/AIDS vaccine.

REFERENCE[1]

SP-1.2, 4.1, HP-13, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Design and develop new or improved vaccine strategies and delivery/production technologies.	1. Existing DNA and viral-vector vaccines strategies require further evaluation	1. (MET) Four newly identified vaccine strategies increased scientific knowledge of how AIDS causes disease and the immune response to it.
FY 2004 1. Initiate one to two multinational trials in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.	1. HIV Vaccine Trials Network currently supports clinical trials at 12 international sites	1. (MET) Two multinational trials initiated in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.
FY 2005 1. Initiate four new Phase I or II trials of new or improved concepts and designs and expand capacity to conduct clinical trials in three international sites.	1. NIH has conducted 68 phase I and phase II HIV vaccine trials to date	1. Performance results will be reported in February 2006.
FY 2006 1. Initiate 1 new phase IIb trial to determine if a third generation vaccine candidate has efficacy.	1. NIH is conducting a phase III trial of a second generation vaccine (canarypox) in Thailand	1. Performance results will be reported in February 2007.

By 2013, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies.

REFERENCE[1]

SP-4.1, HP-5, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Recruit 12 participants for a Phase I trial to evaluate the safety of anti-CD52 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	1. First trial of anti-CD52 to promote tolerance	1. (NOT MET) Anti-CD52 was determined to be unsafe by a non-NIH supported trial of the agent in the target population. Therefore, the opening of the NIH-supported trial was cancelled..
FY 2004 1. Recruit 8-12 participants for a Phase I trial to evaluate the safety of anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	1. First trial of anti-CD3 to promote tolerance	1. (EXT) Protocol for Phase I trial to evaluate anti-CD3 antibody is on hold, pending submission to and review of safety information by the FDA. Target completion is expected in FY 2007 if trial opens in FY 2005.
FY 2005 1. Establish the baseline success rate for islet transplantation, which may impact U.S. Food and Drug Administration (FDA) and Medicare standards of care for islet transplantation. ***Adjusted to:*** Submit response to FDA addressing safety concerns about anti-CD3 antibody.	1. An international multi-center trial of islet transplantation using the Edmonton protocol in patients with type 1 diabetes met the target enrollment of 36 subjects ***Adjusted to:*** First trial of anti-CD3 to promote tolerance.	1. Performance results will be reported in February 2006.

FY 2006 1. Analyze data from phase 1 trial(s) and initiate development of efficacy trial(s), if appropriate. ***Adjusted to:*** Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	1.Phase 1 trial(s) to promote tolerance induction are in protocol development ***Adjusted to:*** First trial of anti-CD3 to promote tolerance.	

FULL COST (dollars in millions)	FY 04	FY 05	FY 06
	$1,516	$1,596	$1,711

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

FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Conduct validation studies of new monkey models of smallpox by employing them in testing of new smallpox vaccines and therapies.	1. Previous non-human primate models of smallpox/orthopox diseases inadequately modeled the progression of human smallpox disease	1. (MET) Human variola and models were tested for protection against disease when administered Modified Ankara (MVA) or Dryvax smallpox vaccines.
FY 2004 1. Expand by 25% the animal model resources available for use by the research community and for licensing products under the FDA Animal Efficacy Rule.	1. 8 animal models available	1. (MET) Two new models of viral hemorrhagic fevers and encephlitides, a model of flea-borne plague transmission, and two models of West Nile virus (Category B agent) have been developed.

	By 2005, develop improved animal models that best recapitulate Parkinson's disease (PD), based on emerging scientific findings of genetic or environmental influences or interactions of genes and the environment on the development of PD.	**REFERENCE**[1]

FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Establish a mouse model repository at a Morris K. Udall Center of Excellence for Parkinson's Disease Research to house PD genetic models and make them available to the PD research community.	1. No repository with this specific housing and distribution capacity exists for PD research	1. (MET) Mouse model repository to house PD genetic models established.
FY 2004 1. Determine if slowing the metabolism of rotenone through cytochrome P-450 inhibition facilitates creation of a mouse model for PD. ***Adjusted to:*** Conduct dose response studies of chronic rotenone administration in normal mice and assess resulting changes in striatal dopamine levels and the number of dopamine neurons in substantia nigra.	1. Cytochrome P-450 accelerates rotenone metabolism in mice so that the PD phenotype cannot be shown	1. (MET) Provided proof of concept in mouse model by administering rotenone and achieving 30-40% depletion of dopamine in striatal terminal fields with clear evidence of degenerating neurons.
FY 2005 1. Combine the mouse model with at least one genetic model of PD and assess its interaction with rotenone.	1. A rotenone mouse model is not yet available	1. Performance results will be reported in February 2006.

FULL COST (dollars in millions)	FY 04	FY 05	FY 06
	$95	$9	$0

SRO-5.1	**By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens.**	**REFERENCE**[1] SP-4.1, HP-13, Outcome

FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Increase the ability of resource-poor countries to conduct clinical trials for the treatment and	1. 12 AACTG sites and 10 PACTG sites	1. (MET) Sites in resource-poor countries are better able to conduct HIV clinical trials as a result of training.

prevention of HIV disease by providing training and capacity building at 4 sites.		
FY 2004 1. Participate in the development of two agents for the prevention or treatment of HIV-associated manifestations, such as co-infections, opportunistic infections, cancers, neurological disorders, or organ-specific complications.	1. 23 approved antiretroviral drugs exist for HIV infection treatment	1. (MET) NIH has supported studies to develop treatments for three HIV-associated manifestations, hepatitis C virus (HCV), Cryptococcal meningitis (CM) and central nervous system (CNS)-associated neurological disease in individuals with HIV.
FY 2005 1. Initiate clinical trials of new anti-HIV drugs and/or anti-HIV multidrug regimens in U.S. and international clinical trial sites.	1. Clinical trials for the next generation of fusion inhibitors and lead compounds representing integrase inhibitors are being completed	1. Performance results will be reported in February 2006.
FY 2006 1. Evaluate interventions to reduce mother to child transmission (MTCT) of HIV and assess the impact of these interventions on future treatment options for women and children.	1. Antiretroviral therapy has dramatically reduced MTCT in the developed world; many developing countries are implementing preventive MTCT programs using nevirapine and other antiretroviral regimens	1. Performance results will be reported in February 2007.
^ ^ . 2 **By 2009, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).**		**REFERENCE** SP-4.1, HP-12, Outcome
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Complete the training of personnel involved in conducting the trial, including sonographers and those operating the Interactive Voice Response System.	1. Standard operating procedures are being completed but training not yet done	1. (MET) Training of all appointed sonographers has been completed.
FY 2004 1. Launch patient enrollment in at least 10 of the 20 planned sites.	1. Protocol for patient enrollment established	1. (MET) There are currently 16 sites actively recruiting patients into the study.
FY 2005 1. Conduct ancillary studies, leveraging the investment of the trial in areas related to the determination of the efficacy of statins in preventing progression of atherosclerosis in children with lupus.	1. One ancillary study approved to assess the effect of statins on blood cells	1. Performance results will be reported in February 2006.
FY 2006 1. Complete baseline data analysis on the enrolled patients, including any adverse events.	1. 14% of patients are enrolled and data analysis of enrolled patients is complete, including any adverse events	1. Performance results will be reported in February 2007.
^ ^ . 3 **By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.**		**REFERENCE** SP-4.1, Outcome, PART
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Fund two additional Centers of Excellence for Chemical Methods and Library Development to develop chemical libraries and high-throughput methods for screening potential therapeutic compounds.	1. Prior to FY 2003, only two centers existed	1. (MET) Two additional Centers of Excellence for Chemical Methods and Library Development were established at Harvard Medical School and the University of Kansas.

FY 2004 1. Investigate at least six innovative methods to synthesize chemical libraries and employ successful methods to create new libraries through the funded Centers. Ensure that inventories of libraries and methods are established so that the successful results of this work can be readily accessible to the scientific community for dry development.	1. High throughput methods for making chemical libraries for drug development are limited	1.(MET) Established CMLD centers investigated at least ten (10) innovative methods to synthesize new chemical libraries while making results of these new libraries and successful methods available to the scientific community.
FY 2005 1. Facilitate the identification of promising therapeutic compounds by funding the biological screening of chemical compounds contained in the libraries and provide an inventory of the results.	1. CMLD centers are currently being established; screening of their libraries has not yet begun	1. Performance results will be reported in February 2006.
FY 2006 1. Begin development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products).	1. Due to the expense and the time required to isolate, purify, and identify new compounds, few pharmaceutical companies include natural products in their drug discovery programs	1. Performance results will be reported in February 2007.

SRO-5.4	**By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.**	**REFERENCE[1]**

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Expand the National Cooperative Drug Discovery Group Program model to target mental disorders and nicotine addiction to advance the development/testing of fundamentally new medications/treatments for mental disorders and nicotine addiction.	1. None of the NCDDG Programs focus on mood disorders and nicotine addiction	1. (MET) Three grants modeled on the National Cooperative Drug Discovery Group (NCDDG) Program were awarded for development/testing of new medications/treatments for mental disorders and nicotine addiction. Prior to these awards, the NCDDG did not address these conditions.
FY 2004 1. Identify potential research tools and drug leads for neurological disorders by developing/utilizing high-throughput screening programs, including assay development.	1. 1,040 FDA-approved drugs and >23,000 potential anti-epileptic compounds screened	1. (MET) 76 promising compounds identified in various assays; 2 potential epileptic therapies advanced to clinical testing. Proof-of-concept tests initiated for alcohol abuse and addiction screening.
FY 2005 1. Create a publicly available collection of 750 bioactive compounds, with defined activity in the nervous system, from industry, academia, and government sources, to be used in screens for potential drugs, research tools, and diagnostic agents.	1. Known bioactive compounds require further evaluation of activity and improved availability	1. Performance results will be reported in February 2006.
FY 2006 1. Test the ability of at least one promising compound to extend survival and reverse molecular effects of SMA in a mouse model of the disorder.	1. SMA program established; 3 promising compounds identified in screens; SMA mouse models available	1. Performance results will be reported in February 2007.

	By 2008 develop and test two new evidence-based treatment approaches	**REFERENCE[1]**
		SP—3.4; HP—26, 27, Outcome.

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2004 1. Adapt two treatment approaches from small-scale research settings to community-based settings for the purpose of bringing research-based treatments to communities.	1. No randomized clinical trials have delivered BSFT and Seeking Safety to these specialized populations	1. (MET) Three treatments have been adapted for community-based settings.

FY 2005 1. Build capacity for targeted treatments by training 90 treatment providers to: (a) participate in clinical trials to promote treatment fidelity; and (b) deliver evidenced-based behavioral treatment to target populations in community settings.	1. Less than 25 treatment providers have been trained to deliver BSFT and Seeking Safety to these specialized populations in randomized clinical trials in community settings	1. Performance results will be reported in February 2006.
FY 2006 1. Recruit approximately 1050 patients from specialized populations to test the efficacy of the two community-based treatments.	1. Enrolment of 350 subjects for Seeking Safety protocol begins in 1st quarter 04. Enrolment of 700 subjects for BSFT protocol begins in 3rd quarter 04	1. Performance results will be reported in February 2007.

	FY 04	FY 05	FY 06
T7TTT T f, ft^:V 1 1 1 1 V V 7. < 1 ^uunciis ill millions)	$835	$829	$798

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

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Expand the genomic resources available to vision researchers through NEIBank and related trans-NIH activities.	1. 31,000 human gene sequences; 12,000 unique human eye-expressed genes	1. (MET) Genomic resources expanded to include 30% more human gene sequences, 8% more unique human eye-expressed genes, and new DNA sequence data and clones.
FY 2004 1. Reach consensus on a descriptive manual with standards that can be used to describe the diverse retinal phenotypes found in macular degeneration.	1. No consensus descriptions on AMD phenotypes exist	1. (MET) A consensus was reached on a manual of classification standards for use by fundus photograph and reading centers that will aide in maintaining useful classification systems to identify new phenotypes and allow for possible meta-analysis of retinal phenotype collections.
FY 2005 1. Collect and make available to investigators genetic material and information from over 4,000 well-characterized patients with either AMD or glaucoma.	1. DNA specimens from large numbers of well-characterized AMD or glaucoma patients are not available	1. Performance results will be reported in February 2006.
FY 2006 1. Develop animal models of AMD and glaucoma that closely mimic the pathologic processes underlying these diseases in humans.	1. Existing animal model systems for AMD and glaucoma do not closely resemble the human disease	1. Performance results will be reported in February 2007.

| 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.**	**REFERENCE**[1] SP-1.1, 4.1, HP-4, 5, 12, Outcome, PART

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Assess the effect of intensive versus conventional glycemic control on intima media thickening of the carotid artery, a marker for progression of atherosclerosis, in participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.	1. No effect of intensive vs. conventional blood glucose control was seen in earlier carotid ultrasound measurements	1. (MET) Effects of intensive versus conventional glycemic control were assessed in EDIC study participants. Finding suggests that aggressive management of blood glucose levels can produce short- and long-term benefits.
FY 2004 1. Complete recruitment for the Action for Health in Diabetes (Look AHEAD) study (5,000 patients), in order to compare the effects on cardiovascular events of an intensive lifestyle intervention designed to achieve and sustain weight loss versus support and education in obese individuals with type 2 diabetes.	1. Look AHEAD had recruited about half (2,500) of its patients	1. (MET) Look AHEAD exceeded its target goal of 5000 obese patients who have type 2 diabetes, and enrolled 5,145 participants by May 2004.

FY 2005 1. Complete recruitment for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (10,000 patients), which is comparing effects on CVD of intensive versus conventional interventions of lowering blood glucose, blood pressure; and treating blood lipids in diabetic patients at high risk for CVD.	1. ACCORD had recruited 1,184 participants in a Vanguard phase	1. Performance results will be reported in February 2006.
FY 2006 1. Look AHE success of interventio such as dia and fitness AD aims to report outcome data on the the one-year intensive weight loss	1. Information is not available regarding the impact of a one-year intensive weight loss intervention on these parameters in a similar diabetic population	1. Performance results will be reported in February 2007.

SRO-6.3	**By 2012, develop a knowledge base on chemical effects in biological systems using a systems biology or toxicogenomics approach.**	**REFERENCE[1]** SP^f 1 HP^ O$_{u}$t$_{come}$

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Launch a pilot prototype database project to test the design and implementation of the knowledge base components and system architecture.	1. Intramural databases and commercial software to build ProtoCEBS available	1. (MET) ProtoCEBS launched, tested, and implemented.
FY 2004 1. Create the capability to import, export, and link molecular expression data by extending the Chemical Effects in Biological Systems (CEBS) database object model to include toxicology/pathology fields and by creating a data portal that will load toxicology data.	1. CEBS object model to capture molecular expression data (only) designed but not tested	1. (MET) CEBS now has a data portal that loads toxicology data. CEBS can import, export, and link molecular expression data to toxicology/pathology fields.
FY 2005 1. Create and provide public access to a global molecular expression and toxicology/pathology database of environmental chemicals and drugs (CEBS) featuring simple query download capability.	1. CEBS version 1.0 launched in August 2003 contains only microarray data	1. Performance results will be reported in February 2006.
FY 2006 1. Enhance the CEBS to allow the capture and integration of transcriptomics, proteomics, and toxicologic data for the same compound.	1. The CEBS is limited to individual data sets and cannot integrate data from multiple data sets for a single compound	1. Performance results will be reported in February 2007.

FULL COST (dollars in millions)	FY 04	FY 05	FY 06
	$98	$72	$82

SRO^1	**By 2005, evaluate 10 commonly used botanicals for inhibition/induction of enzymes that metabolize drugs as a method of identifying potential botanical drug interactions.**	**REFERENCE[1]** SP-2.2, 4.1, 5.1, Outcome, Efficiency

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Identify results of studies on three botanicals that show inhibition/induction of enzymes that metabolize drugs.	1. Some characterization of St. John's wort; very little known about other botanicals	1. (MET) Effects were observed on selected botanical extracts on the inhibition or induction of selected enzymes that metabolize drugs.
FY 2004 1. Identify results of studies on three additional botanicals that show inhibition/induction of enzymes that metabolize drugs.	1. St. John's wort better characterized. Good characterization of ginkgo, garlic, saw palmetto, 2 species of ginseng, and PC-SPES	1. (MET) Effects were observed on three selected botanical extracts on the inhibition or induction of selected enzymes that metabolize drugs.
FY 2005 1. Identify results of studies on four additional botanicals that show inhibition/induction of enzymes that metabolize drugs.	1. Characterization of additional botanicals from FY 2004	1. Performance results will be reported in February 2006.

SRO-7.2	By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.	REFERENCE[1]
		SP-4.1, 4.2, HP-3, Outcome, Efficiency, PART

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Establish intramural and extramural collaborations to select and employ substrate nanotechnology fabrication techniques to enable high-throughput and highly reliable/reproducible proteomic analyses.	1. Lack of relevant collaborations	1. (MET) Collaborations established and work progressing on employing nanotechnology techniques to enable high-throughput proteomic analyses relevant to early detection of cancer.
FY 2004 1. Establish a core laboratory at NIH to bring together extramural and intramural fabrication technologies with the capability to derive targets, identify the most promising applications for combined functionalized nanoparticles, and steward therapeutic nanotechnologies through validation.	1. No current core laboratory with needed capacity	1. (MET) The national Nanotechnology Characterization Laboratory (NCL) has been established and will enable development of essential data about the profiles of nanoparticles in biological systems.
FY 2005 1. Integrate nanosensors and nanoparticles into a platform technology for development in applied research settings.	1. Existing nanosensors and nanoparticles not integrated into a common platform	1. Performance results will be reported in February 2006.
FY 2006 1. Integration of nanotechnology-based components into a system capable of detecting biomarkers *in vitro*.	1. Nanocantilevers, nanowires, and nanochannels currently in development, but not yet tested for cancer detection, imaging, and treatment *in vitro*	1. Performance results will be reported in February 2007.

	By 2005, create the next-generation map of the human genome, a so-called haplotype map ("HapMap"), by identifying the patterns of genetic variation across all human chromosomes.	REFERENCE[1]

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

FULL COST (dollars in millions)	FY 04	FY 05	FY 06
	$30	$13	$12

	By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases.	REFERENCE[1]
		SP-1.2, 2.1, 4.1, HP-10, 14, 24, 25, Outcome, Efficiency

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Complete the genomic sequences of at least five bacteria and two protozoa that cause infectious disease.	1. Genome sequences for 29 bacterial pathogens, 1 protozoan parasite, and 1 insect completed	1. (MET): Genomic sequences were identified for 8 bacterial pathogens and 3 protozoans.
FY 2004 1. Complete the genomic sequences of at least three fungal pathogens, five bacterial pathogens, and two protozoa that cause infectious disease.	1. Genome sequences for 40 bacterial pathogens, 4 protozoan parasites, and 1 insect completed	1. (MET) Genomic sequences were identified for 18 bacteria, 4 protozoan parasites, and 3 fungi.
FY 2005 1. Complete the genomic sequences of at least two fungal pathogens, five bacterial pathogens, and four protozoa that cause infectious disease.	1. Genome sequences for 58 bacterial pathogens, 8 protozoan parasites, 3 fungi, and 1 insect completed	1. Performance results will be reported in February 2006.
FY 2006 1. Complete the genome sequence of at least one fungal pathogen, six bacterial pathogens, two protozoan parasites, and one invertebrate vector of infectious diseases.	1. Genome sequences for 63 bacterial pathogens, 12 protozoan parasites, 5 fungi, and 1 invertebrate vectors of infectious diseases completed	1. Performance results will be reported in February 2007.

SRO-8.2	By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals.	REFERENCE[1] SP-4.1,6.2, HP-2, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Characterize effects of the bone protein thrombospondin-2 on the generation of bone-forming cells from precursor cells in the bone marrow and identify regions of the thrombospondin-2 molecule that are required for the effects.	1. Information on the role of thrombospondin-2 in bone generation is incomplete	1. (MET) Thrombospondin-2 promotes bone formation in the early stage of cell differentiation; functional elements at one end of molecule responsible for this effect.
FY 2004 1. Identify biochemical pathways in bone-forming cells that are responsible for extended survival of cells on interaction with the bone protein osteonectin.	1. Biochemical pathways that mediate cell survival are unknown	1. (MET) Results suggest that the interaction of bone-forming cells with osteonectin enhances cell survival through activation of the Wnt pathway.
FY 2005 1. Identify regions of bone and bone marrow in which thrombospondin-2 is produced under conditions of bone loss and bone formation. Generate a genetically altered mouse strain in which a fluorescent protein is produced under the control of the same genetic elements that control the production of thrombospondin-2.	1. Information incomplete on where thrombospondin-2 is produced; mouse model can provide this data	1. Performance results will be reported in February 2006.
FY 2006 1. Generate a genetically modified mouse in which only bone-forming cells are deficient in fibronectin, and identify the cell surface molecule mediating interaction between bone-forming cells and connective tissue growth factor.	1. Mice wholly deficient in fibronectin are not viable. Molecules interacting with CTGF are unknown	1. Performance results will be reported in February 2007.

SRO-8.3	**By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, nonredundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA) transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms.**	**REFERENCE[1]** SP-4.1, Outcome, Efficiency

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Make the RefSeq Collection database available for downloading to enable commercial or academic groups to perform exhaustive analyses across the entire RefSeq Collection data set.	1. At the end of FY02, the RefSeq collection included 446,000 proteins and was not available for FTP	1. (MET) The RefSeq collection was made available on a regular release cycle to scientists at commercial and academic sites for downloading and analysis of the entire data set.
FY 2004 1. Develop the infrastructure to support wider access to the RefSeq Collection via the Internet to provide users with a centralized set of annotated sequence information.	1. RefSeq collection includes sequence data from 2124 species; only a limited database is available	1. (MET) The RefSeq collection is now fully available via the online resource Entrez Gene.
FY 2005 1. Expand the project to include outside groups to increase the amount of sequence and functional information in the database. Collaborations will provide additional reference sequence records, whole-genome annotation, functional annotation of multigene families, and expert review of single genes.	1. About 40 collaborations in place for obtaining annotated RefSeq records and other functional data	1. Performance results will be reported in February 2006.

SRO-8.4	**By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding.**	**REFERENCE[1]** SP-4.3, HP-23, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Develop a data collection and management system to allow for the retrieval of potential target indicators to evaluate the impact of the IDeA/Centers of Biomedical Research Excellence (COBRE) Program.	1. Indicators from previous evaluations and pre-COBRE analysis and previous evaluations	1. (MET) Data collection and management system in place for retrieval of potential target indicators related to evaluating impact of IDeA/Centers of Biomedical Research Excellence Program.
FY 2004 Assessment Methodology for IDeA Program (Step 1): • Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/COBRE impact. • Develop a data collection system for BRIN.	• Data collection and management system to evaluate impact of IDeA/COBRE in place • Indicators from IDeA/COBRE evaluation design	1. (MET) The COBRE evaluation design, which includes a confirmed list of target indicators, is complete. Data collection and management system is in place for BRIN.
FY 2005 Assessment Methodology for IDeA Program (Step 2): • Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/BRIN impact. • Assess results of COBRE evaluation design study.	• Data collection and management system to evaluate impact of IDeA/BRIN in place • COBRE evaluation design completed but not evaluated	1. Performance results will be reported in February 2006.
FY 2006 1. Full-Scale Assessment of the IDeA Program (Step 1): • Initiate the full-scale evaluation for IDeA/COBRE	1. COBRE evaluation design	1. Performance results will be reported in February 2007.

	By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease.	REFERENCE[1]
		*[1], SP-4.1, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2005 1. Identify specific domains to be measured, evaluate existing measures and items, and develop instrument(s) and assessment methods for use in diverse chronic disease patient samples.	1. Highly valid, reliable, and broadly usable assessment tools are needed to enhance clinical research on patient-reported chronic disease outcomes.	1. Performance results will be reported in February 2006.
FY 2006 1. Initiate administration of instrument(s) to a large demographically diverse patient sample representing a wide range of chronic disease type and severity.	1. An initial item pool for assessing specified domains of symptoms and/or domains of health-related quality of life developed using FY 04 target.	1. Performance results will be reported in February 2007.

FULL COST (dollars in millions)	FY 04	FY 05	FY 06
	$00	$313	$334

	By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the United States by 10% by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes).	REFERENCE[1]
		SP-4.1, 6.2, HP-5,12,18, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Identify at least one biological (e.g., gene-environment) interaction that has high probability of contributing to depression.	1. Known that stress linked to depression but interaction not known	1. (MET) A link was made between a specific gene-environment interaction (5-HTT and high stress) and vulnerability to depression.
FY 2004 1. Determine whether vascular changes related to aging contribute to depression.	1. Subcortical lesions, common in elderly with depression and in vascular disease, are being studied as potential cause of depression	1. (MET) A strong correlation has been found between vascular changes resulting in unique lesions in the brain and depression in elderly patients.
FY 2005 1. Determine at least four characteristics that help identify subgroups of people with depression who respond differentially to existing treatments.	1. A series of clinical trials are currently underway that match patients' responses to different treatments	1. Performance results will be reported in February 2006.
FY 2006 1. Identify at least one effective strategy for treating depressiori in the elderly in a variety of settings.	1. A number of interventions to treat depression in the elderly are currently being developed and tested	1. Performance results will be reported in February 2007.

SRO-9.2	By 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities.	REFERENCE[1]
		SP_L1 3^ 4^ HP—^ ^ Oiiteom^ Effi$_{ency}$

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Establish a 5-year program to create 12 to 14 Partnership Centers to Reduce Health Disparities that will focus on influential factors that reduce health disparities.	1. Piloted programs to build nursing center research capacity focused on health disparities	1. (MET) Seventeen Nursing Partnership Centers established to reduce health disparities, including stroke, which link research-experienced nursing schools with minority-serving nursing schools across the nation.
FY 2004 1. Establish a minority-focused, acute stroke research and care center to conduct a study of the epidemiology of stroke, barriers to acute stroke care, and quality of care within the specific racial/ethnic communities being served by the care center.	1. Acute stroke center exists but is not focused on stroke disparities or in a minority community	1. (MET) Acute stroke care center serving a minority community in the Washington DC metropolitan area has been established.

FY 2005 1. Establish the infrastructure for a Stroke Prevention and Intervention Research Program at a minority institution.	1. Minority institution research /training programs exist but not on stroke prevention/intervention	1. Performance results will be reported in February 2006.
FY 2006 1. Establish the infrastructure for a pilot Alaska Native Stroke registry that will facilitate identifying risk factors and strategies to improve stroke prevention and quality of stroke care provided to Alaska Natives.	1. Several registries for Alaska Natives exist, including for cancer and diabetes, but none for stroke	1. Performance results will be reported in February 2007.

FULL COST (dollars in millions)	FY 04	FY 05	FY 06
	$107	$107	$84

[1] SP-# Indicates the DHHS Strategic Plan goal to which each GPRA goal pertains.
HP-# Indicates the Focus Area of *Healthy People 2010* to which each goal pertains.
PART-Indicates goal has been examined by Program Assessment Rating Tool (PART)

• COMMUNICATION AND TRANSFER OF RESULTS

CTR-1	**By 2008, reduce the disparity between African American and white infants in back sleeping by 50% to further reduce the risk of sudden infant death syndrome (SIDS).**	REFERENCE[1] SP-3.4, HP-11, 16, Outcome, Efficiency

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. In collaboration with African American organizations, community health and other local officials, and faith-based organizations, conduct regional summit meetings to train and motivate individuals who will implement SIDS risk reduction activities in their communities.	1. No regional summit meetings were held prior to 2003	1. (MET) Over 1,000 participants were trained and motivated to reduce SIDS in African American communities during 3 regional U.S. summits.
FY 2004 1. Conduct 250 interviews among the approximately 1,500 participants who attended the three summit meetings held in 2003 to determine that each summit resulted in a minimum of 50 outreach activities.	1. No interviews have been conducted for this purpose	1. (MET) Interviews were held with participants from each summit and 150 outreach activities resulted from each of the summits.
FY 2005 1. Continue to extend "Back to Sleep" campaign messages to African American populations through community-based collaborations/partnerships by involving a minimum of six national organizations in SIDS training and educational activities.	1. Three participating national organizations	1. Performance results will be reported in February 2006.
FY 2006 1. Promote a continuing education module with at least six national nursing organizations serving African American communities to extend the *Back to Sleep* campaign messages.	1. There are no known efforts to systematically educate the nursing community on national level about SIDS risk reduction	1. Performance results will be reported in February 2007.

CTR 2	**By 2006, Increase awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least five communities and extending the impact of the campaign, "Know Stroke. Know the Signs. Act in Time."**	REFERENCE[1]

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2004 1. Work with partners in five communities each with at least 15 percent African American population to extend the "Know Stroke" campaign messages by attending community fairs and collaborating with local leaders and health educators to disseminate 3,000 "Know Stroke" community education kits and	1. National partnerships developed; no current comprehensive local partnerships	1. (MET) Completed outreach programs in 5 U.S. cities. Distributed 109,619 brochures, including 27,236 to African American audiences. Distributed 3,000 kits through national marketing campaign to city and county health officials.

100,000 "Know Stroke" brochures (25,000 will be distributed to African American audiences).		
FY 2005 1. Extend the outreach program to an additional five communities nationwide, arming community leaders with tools and information to distribute an additional 5,000 "Know Stroke" community education kits (1,000 will be through African American partners).	1. Partnerships developed in FY 2004.	1. Performance results will be reported in February 2006.
FY 2006 1. Work with national organizations such as the CDC, the National Council of La Raza, and the Urban League to develop community-based programs for extending the Know Stroke messages to Hispanics and African Americans in at least 10 markets.	1. Partnerships established through community based outreach in FY 2004	1. Performance results will be reported in February 2007.

CTR 3	**Through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products. (Ongoing)**	REFERENCE[1]
		SP-4.4, Output

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2004 1. Develop a needs assessment study for a technical assistance program in technology transfer for developing countries to systematically detail the nature and extent of issues that the TA program should address.	1. No known needs assessment studies exist for developing technology TA program	1. (EXT) Funding was not approved, although international partners and personnel were secured to initiate the TA program.
FY 2005 1. Based on results of the needs assessment, recruit and select personnel to design and implement the technical assistance program.	1. No personnel	1. Performance results will be reported in February 2006.
2. Identify and target appropriate institutions in at least three developing countries in order to educate members on adapting and building infrastructure for transferring laboratory discoveries to the bedside.	2. Limited access to targeted training in developing countries	2. Performance results will be reported in February 2006.
FY 2006 1. Secure potential supporting partner(s) to support the onset of the technical assistance program.	1. While no organizations have been formally approached to serve as partners in supporting the technical assistance program, we have informally discussed synergies and potential advantages of working with different organizations while participating in domestic and foreign meetings	2. Performance results will be reported in February 2007.

CTR 4	**Increase the percentage of Small Business Innovative Research (SBIR) Program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization. (Ongoing)**	REFERENCE[1]
		SP-4.2, 4.4, Outcome

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2004 1. Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization (FY 04) CAP	1. No current programs	1. (MET) Completed Pilot CAP with 50 participants. Selected vendor for pilot Niche Assessment Program.
2. Implement effective piloted programs to create a menu of technical assistance programs	2. CAP Pilot	2. (MET) Initiated trans-NIH CAP with 130 participants.
3. Report critical elements to assess advances of each technical assistance program	3. TBD in FY04 CAP pilot conversion to program implementation	3. (MET) Pilot CAP-- 50 participants of which 35 presented business opportunity at investment event. At 6 month mark, 33% had increased sales or were in negotiation.
FY 2005 1. Pilot test specific technical assistance program(s) to further development of SBIR projects toward	1. No current programs	1. Performance results will be reported in February 2006.

commercialization (FY 05) Niche Assessment		
2. Implement effective piloted programs to create a menu of technical assistance programs	2. CAP Pilot	2. Performance results will be reported in February 2006.
3. Report critical elements to assess advances of each technical assistance program	3. TBD in FY04 CAP pilot conversion to program implementation	3. Performance results will be reported in February 2006.
FY 2006 1. Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization (FY 06) Manufacturing or FDA Regulatory Assistance	1. No current programs	1. Performance results will be reported in February 2007.
2. Implement effective piloted programs to create a menu of technical assistance programs	2. CAP Pilot	2. Performance results will be reported in February 2007.
3. Report critical elements to assess advances of each technical assistance program	3. TBD in FY04 CAP pilot conversion to program implementation	1. Performance results will be reported in February 2007.

FULL COST (dollars in millions)	FY 04	FY 05	FY 06
	$4	$4	$4

[1] SP-#: Indicates the DHHS Strategic Plan goal to which each GPRA goal pertains.
HP-#: Indicates the Focus Area of "Healthy People 2010" to which each goal pertains.

• CAPACITY BUILDING AND RESEARCH RESOURCES

	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. (Ongoing)	**REFERENCE[1]**
		SP—43, HP-23, Output

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2004 1. Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH research grants exceeds relevant comparison groups by 10% within 10 years of graduation.	1. Award rates NRSA Group: 46% Comparison Group A: 35% Comparison Group B: 26%	1. (MET) Award rate to comparison groups exceeded by 12%
2. Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH research grants exceeds relevant comparison groups by 10% within 10 years of termination.	2. Applied for but did not receive= 174 recipients; 929 trainees Received last year of training support 10 years before: 324 recipients; 808 trainees	2. (MET) Award rate to comparison groups exceeded by 14%
3. Ensure that there is multidisciplinary/ interdisciplinary training on at least 10% of all training grants as evidenced by trainees reporting different Field of Training or Discipline/Specialty Field codes or departments.	3. 486 multidisciplinary grants	3. (MET) The reported rate of multidisciplinary grants was 44%
4. Achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research. 120 K23 awards for FY03-FY06 50 K24 awards for FY03-FY06	4. (FY02) Awards granted K23 645 K24 263 K30 59	4. (MET) All annual targets for recruiting individuals into clinical research achieved. K23 222 (exceeded target of 120 by 102) K24 50 K30 59 (exceeded target of 50 by 9)

	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. (Ongoing)	REFERENCE[1]
		SP-4.3, HP-23, Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
50 K30 awards for FY03-FY06		
5. Increase by 1% over baseline the number of research training and career development positions occupied and enhanced opportunities provided to individuals from underrepresented racial and ethnic groups.	5. (FY03) Asian: 2,415 African American = 1,466 American Indian = 135 Pacific Islander[3] =72 Hispanic[4]= 975	5. (EXT) Comparable statistics run every May; hence, annually reported measures to be re-configured to complete reporting in December of the reporting year.
6. Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	6. Applications received= 1,881 Contracts awarded= 1,193	6. (MET) Applications received= 2,498 Contracts awarded= 1,407 (56% of Applicants were awarded contracts)
FY 2005 1. Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH research grants exceeds relevant comparison groups by 10% within 10 years of graduation.	1. Award rates NRSA Group: 46% Comparison Group A: 35% Comparison Group B: 26%	1. Performance results will be reported in February 2006.
2. Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH research grants exceeds relevant comparison groups by 10% within 10 years of termination.	2. Applied for but did not receive= 174 recipients; 929 trainees Received last year of training support 10 years before: 324 recipients; 808 trainees	2. Performance results will be reported in February 2006.
3. Ensure that there is multidisciplinary/interdisciplinary training on at least 10% of all training grants as evidenced by trainees reporting different Field of Training or Discipline/Specialty Field codes or departments.	3. 486 multidisciplinary grants	3. Performance results will be reported in February 2006.
4. Achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research. 120 K23 awards for FY03-FY06 50 K24 awards for FY03-FY06 50 K30 awards for FY03-FY06	4. (FY99-FY02) Awards granted K23 645 K24 263 K30 59	4. Performance results will be reported in February 2006.
5. Increase by 1% over baseline the number of research training and career development positions occupied and enhanced opportunities provided to individuals from underrepresented racial and ethnic groups.	5. (FY03) Asian: 2,415 African American = 1,466 American Indian = 135 Pacific Islander[3] =72 Hispanic[4]= 975	5. Performance results will be reported in February 2006.
6. Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	6. Applications received= 1,881 Contracts awarded= 1,193	6. Performance results will be reported in February 2006.
FY 2006 1. Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH research grants exceeds relevant comparison groups by 10% within 10 years of graduation.	1. Award rates NRSA Group: 46% Comparison Group A: 35% Comparison Group B: 26%	1. Performance results will be reported in February 2007.

[1] OMB accepted the recommendations of the Interagency Committee for the Review of the Racial and Ethnic Standards with the following two modifications: (1) the Asian or Pacific Islander category will be separated into two categories -- "Asian" and "Native Hawaiian or Other Pacific Islander," and (2) the term "Hispanic" will be changed to "Hispanic or Latino." The revised standards will have five minimum categories for data on race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. There will be two categories for data on ethnicity: "Hispanic or Latino" and "Not Hispanic or Latino."

[2] OMB Statistical Policy Directive No.15, indicates that Hispanic is an ethnicity. Therefore, information given on the Hispanic category should not be compared with race data. There may be duplicative counting with racial groups.

[3] OMB accepted the recommendations of the Interagency Committee for the Review of the Racial and Ethnic Standards with the following two modifications: (1) the Asian or Pacific Islander category will be separated into two categories -- "Asian" and "Native Hawaiian or Other Pacific Islander," and (2) the term "Hispanic" will be changed to "Hispanic or Latino." The revised standards will have five minimum categories for data on race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. There will be two categories for data on ethnicity: "Hispanic or Latino" and "Not Hispanic or Latino."

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	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. (Ongoing)	REFERENCE[1]
		SP-4.3, HP-23, Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
2. Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH research grants exceeds relevant comparison groups by 10% within 10 years of termination.	2. Applied for but did not receive= 174 recipients; 929 trainees Received last year of training support 10 years before: 324 recipients; 808 trainees	2. Performance results will be reported in February 2007.
3. Ensure that there is multidisciplinary/interdisciplinary training on at least 10% of all training grants as evidenced by trainees reporting different Field of Training or Discipline/Specialty Field codes or departments.	3. 486 multidisciplinary grants	3. Performance results will be reported in February 2007.
4. Achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research. 120 K23 awards for FY03-FY06 50 K24 awards for FY03-FY06 50 K30 awards for FY03-FY06	4. (FY99-FY02) Awards granted K23 645 K24 263 K30 59	4. Performance results will be reported in February 2007.
5. Increase by 1% over baseline the number of research training and career development positions occupied and enhanced opportunities provided to individuals from underrepresented racial and ethnic groups.	5. (FY03) Asian: 2,415 African American = 1,466 American Indian = 135 Pacific Islander[1] =72 Hispanic[2]= 975	5. Performance results will be reported in February 2007.
6. Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	6. Applications received= 1,881 Contracts awarded= 1,193	6. Performance results will be reported in February 2007.

CBRR-2	Promote data sharing and provide information in real time by implementing and monitoring the NIH Business System. (By FY 2010, the NBRSS will be in an ongoing status.)	REFERENCE[1]
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Deploy the general ledger/budgeting module.	1. NBS without general ledger/budget module	1. (MET) General ledger/budgeting module deployed.
2. Deploy the property module.	2. NBS without property module	2. (EXT) Further analysis of the system is needed. Extended to February 2005. Performance results will be reported in February 2006.
3. Deploy the travel module.	3. NBS without travel module	3. (MET) Travel module deployed.
FY 2004 1. Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development'	1. NBS without contracts/acquisition/accounts payable/supply modules	1. (MET) Completed system design and configuration, unit beta testing and commenced CRP1 testing.
2. Deploy the property module.	2. NBS without property module.	2 . (EXT) Extended to February 2005, after which goal reporting will be covered by target 4 (see narrative)
3. Deploy the service and supply fund activities module. FY04 Program steps a-e 'Development'	3. NBS without service and supply fund activities module.	3. (MET) Identified solutions for automated amortization for Real Property and Agency Agreements.

[1] OMB accepted the recommendations of the Interagency Committee for the Review of the Racial and Ethnic Standards with the following two modifications: (1) the Asian or Pacific Islander category will be separated into two categories -- "Asian" and "Native Hawaiian or Other Pacific Islander," and (2) the term "Hispanic" will be changed to "Hispanic or Latino." The revised standards will have five minimum categories for data on race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. There will be two categories for data on ethnicity: "Hispanic or Latino" and "Not Hispanic or Latino."

[2] OMB Statistical Policy Directive No.15, indicates that Hispanic is an ethnicity. Therefore, information given on the Hispanic category should not be compared with race data. There may be duplicative counting with racial groups.

FY 2005 1. Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY05 Program steps a-g 'Integration'	1. NBS without contracts/acquisition/accounts payable/supply modules	1. Performance results will be reported in February 2006.
2. Deploy the service and supply fund activities module. FY04 Program steps a-g 'Integration'	2. NBS without service and supply fund activities module.	2. Performance results will be reported in February 2006.
FY 2006 1. Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY06 Program steps h-I 'Final review'	1. NBS without service and supply fund activities module.	1. Performance results will be reported in February 2007.
2. Deploy the service and supply fund activities module. FY06 Program steps h-I 'Final review'	2. NBS without service and supply fund activities module.	2. Performance results will be reported in February 2007.
3. Report critical elements of General Ledger and Travel Module performance	3. NBS performance with General Ledger and Travel Modules deployed	3. Performance results will be reported in February 2007.
	Streamline business processes and automate data movement by implementing, monitoring and updating the Clinical Research Information System (CRIS). (Ongoing)	**REFERENCE**[1] ft1. SP-5.1, 5.2, 5.5, 8.5, Output
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2004 1. Implement a core hospital system.	1. 28 year old legacy system	1. (MET) The core hospital system, CRIS, went live and the legacy system was retired.
FY 2005 1. Implement a surgery and anesthesia management system.	1. No current system exists	1. Performance results will be reported in February 2006.
2. Implement a clinical data warehouse.	2. No trans-NIH clinical data warehouse currently exists	2. Performance results will be reported in February 2006.
FY 2006 1. Integrate clinical systems across NIH intramural programs to eliminate redundancy	1. Multiple redundant clinical systems exist	1. Performance results will be reported in February 2007.
	Provide greater functionality and more streamlined processes in grants administration by developing and monitoring the NIH electronic research administration (eRA). (Ongoing)	**REFERENCE**[1] ft1. SP-8.5, Output, Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Implement electronic progress reporting with all 65 newly online institutions participating in the Federal Demonstration Partnership.	1. No institutions using electronic reporting	1. (MET) Electronic reporting available to the 65 FDP participating institutions.
2. Expand availability of electronic reporting to all grantee institutions.	2. 145 FDP institutions given access to electronic reporting	2. (EXT) Volume testing needed. Extended to third quarter February 2004. Performance results will be reported February 2005.
FY 2004 1. Expand availability of electronic progress reporting to all grantee institutions.	1. (FY02) 145 FDP institutions given access to electronic reporting	1. (MET) 2,800 progress reports electronically and 102 grantee organizations are now registered to submit.
2. Pilot-test eXtensible Markup Language (XML) transmission between extramural community and NIH.	2. Need for system to conform with OMB/Federal Enterprise Architecture	2. (MET) Pilot-tested XML transmissions successful and technology incorporated into eRA architecture stack.
3. Develop plan to integrate OPDIVs.	3. No Plan for OPDIV Integration	3. (MET) eRA has developed plans for adding the FDA and components of the CDC.
FY 2005 1. Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 FY05 - 25% electronic business processing	1. 10% of business processes being done electronically	1. Performance results will be reported in February 2006.
2. Integrate HHS OPDIV's as eRA users for administration of research grants by the end of	2. Integration plan has been developed. Limited use of eRA	2. Performance results will be reported in February 2006.

FY2006. FY05 - 50% of eligible HHS OPDIV's	Grant System by two other HHS OPDIV's, AHRQ and CDC/NIOSH	
3. Begin pilot-testing of progress reporting for multi-project mechanisms.	3. (FY99) 14 simple competing grant applications received	3. Performance results will be reported in February 2006. Extended from 2003 due to XML development.
FY 2006 1. Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 FY06 - 40% electronic business processing	1. 10% of business processes being done electronically	1. Performance results will be reported in February 2007.
2. Integrate HHS OPDIV's as eRA users for administration of research grants by the end of FY2006. FY06 - 100% of eligible HHS OPDIV's	2. Integration plan has been developed. Limited use of eRA Grant System by two other HHS OPDIV's, AHRQ and CDC/NIOSH	2. Performance results will be reported in February 2007.
FULL COST (dollars in millions)	FY 04	FY 05 FY 06
	$1,543	$1,604 $1,635

[1] Jit-Indicates that the goal is part of the President's Management Agenda.
SP-# Indicates the DHHS Strategic Plan goal to which each GPRA goal pertains.

• STRATEGIC MANAGEMENT OF HUMAN CAPITAL

SMHC-3	**Improve the strategic management of NIH human resources by developing and monitoring a comprehensive human capital plan based on the Agency's programmatic objectives and projected future needs. (Ongoing)**	**REFERENCE[1]**
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2004 1. Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.	1. (FY 01) NIH Workforce Plan, June 2001	1. (MET) Recommendations were identified, as potential initiatives, for improving human capital management; in key Intramural Research roles.
2. Conduct a study to identify competencies needed by NIH leaders who will drive future development efforts.	2. (FY 02) Administrative Restructuring Advisory Committee	2. (MET) A major study to identify competencies and success profiles of key Intramural leaders was completed.
FY 2005 1. Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.	1. Performance indicators to be determined from FY 2004 results	1. Performance results will be reported in February 2006.
2. Establish performance indicators with baselines related to recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.	2. Performance indicators to be determined from FY 2004 results	2. Performance results will be reported in February 2006.
FY 2006 1. Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Extramural Research Program.	1. (FY 04) Performance indicators and additional performance indicators to be determined from FY 2005 results	2. Performance results will be reported in February 2007.

2. Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program. (Report on performance indicators and expected enhancements.)	2. (FY 04) Performance indicators and additional performance indicators to be determined from FY 2005 results	2. Performance results will be reported in February 2007.
SMHC-4 **Ensure that NIH commercial functions are performed as efficiently and cost-effectively as possible by conducting competitive sourcing reviews on the required number of functions within the Agency's commercial inventory. (Ongoing)**		**REFERENCE[1]** * SP-8.3, 8.4, Output; Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2003 1. Identify annually commercial activities for competitive sourcing comparison.	1. Preplanning initiated for identifying functional areas	1. (MET) Extramural Administrative Support Services and Real Property Management groups identified for competitive sourcing comparison.
2. Complete negotiated competitive sourcing reviews annually.	2. Functional areas identified as appropriate for review	2. (MET) Competitive sourcing reviews completed for Extramural Administrative Support Services and Real Property Management groups.
FY 2004 1. Identify annually commercial activities for competitive sourcing comparison.	1. Preplanning initiated for identifying functional areas	1. (MET) Nine streamlined and two standard studies conducted in FY 2004.
2. Complete negotiated competitive sourcing reviews annually.	2. Functional areas identified as appropriate for review	2. (MET) Nine streamlined studies completed, with 8 work awards placed with NIH.
3. Implement transition services for employees annually displaced due to prior year's competitive sourcing.	3. Transition plans for employees	3. (MET) Career transition services provided for out-placed staff as a result of competitive assessments/ studies.
FY 2005 1. Identify annually commercial activities for competitive sourcing comparison.	1. Preplanning initiated for identifying functional areas	1. Performance results will be reported in February 2006.
2. Complete negotiated competitive sourcing reviews annually.	2. Functional areas identified as appropriate for review	2. Performance results will be reported in February 2006.
3. Evaluate transition services provided to employees.	3. Transition plans for employees	3. Performance results will be reported in February 2006.
FY 2006 1. Identify annually commercial activities for competitive sourcing comparison.	1. Preplanning initiated for identifying functional areas	1. Performance results will be reported in February 2007.
2. Complete negotiated competitive sourcing reviews annually.	2. Functional areas identified as appropriate for review	2. Performance results will be reported in February 2007.
SMHC5 **Improve and monitor the use of human resource services by providing real-time access to tools via the NIH Portal. (Ongoing)**		**REFERENCE[1]** SP-8.5, Output, Efficiency
FY TARGETS	**BASELINE**	**ACTUAL PERFORMANCE**
FY 2005 1. Develop an HR Community on the NIH Portal to become the primary site for NIH HR information, systems and resources.	1. Multiple means of access to HR systems; multiple websites for HR information and resources	1. Performance results will be reported in February 2006.
2. Identify HR critical elements and tools to monitor use and quality of the HR information.	2. Inconsistent quality and currency of HR information	2. Performance results will be reported in February 2006.
FY 2006 1. Establish baselines for the HR critical elements to monitor over time.	1. HR critical elements and tools identified	1. Performance results will be reported in February 2007.
1. Develop a plan for corrective strategies to improve usability and quality of HR information.	2. HR Community established	2. Performance results will be reported in February 2007.

FULL COST (dollars in millions) *excludes SMHC-4.*	FY 04	FY 05	FY 06
	$4	$14	$6

[1] *: Indicates that the goal is part of the President's Management Agenda.
SP-#: Indicates the DHHS Strategic Plan goal to which each GPRA goal pertains.

• PROGRAM OVERSIGHT AND IMPROVEMENT

1 POI-1 Ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing and monitoring an Earned Value Analysis and Management System. (Ongoing)

REFERENCE[1]

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2004 1. Evaluate and assess existing project management systems integrating findings for implementation of a proof-of-concept version of NIH's Earned Value Management System (EVMS).	1. Policies and procedures in place to identify data needed for evaluation	1. (MET) Project Management Systems were evaluated and assessed by ORF staff and EVMS external experts..
FY 2005 1. Implement a revised project management system that incorporates Earned Value Analysis and Management principles to evaluate on time and within budget delivery of projects.	1. EVAMS proof-of-concept version	1. Performance results will be reported in February 2006.
FY 2006 1. Fully launch the Earned Value Management System (EVMS) and conduct Earned Value Analyses to evaluate and assess major capital acquisition projects included in the NIH Real Estate Portfolio.	1. Earned Value Management System (EVMS) is incorporated into the project management system	1. Performance results will be reported in February 2007.

1 POI-2 1 Utilize Performance-Based Contracting (PBC). (Ongoing)

REFERENCE[1]

*. SP-8.4, Output

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Allocate $226 million of available NIH contracting dollars to PBC-eligible contracts.	1. For FY 2002, $207 million projected for contracted work with requirements tied to performance	1. (MET) Over $226 million of NIH-eligible service contracting dollars were allocated to PBC contracts.
FY 2004 1. Obligate 40% of eligible service contracting dollars through PBC.	1. 40% of eligible service contracting dollars were PBC in 2004	1. (MET) Obligated $654 million of eligible service contracting dollars through performance-based contracting.
FY 2005 1. Obligate 40% of eligible service contracting dollars through PBC.	1. 40% of eligible service contracting dollars were PBC in 2004	1. Performance results will be reported in February 2006.
FY 2006 1. Obligate FY 2006 OMB/OFPP Goal of eligible service contracting dollars through PBC.	1. FY 2006 OMB/OFPP Goal	1. Performance results will be reported in February 2007.

1 POI-4 1 By 2005, Ensure proper stewardship of public funding for research.

REFERENCE[1]

SP-8.2, 8.4, 8.6, Output

FY TARGETS	BASELINE	ACTUAL PERFORMANCE
FY 2003 1. Conduct five proactive compliance site visits.	1. Criteria in place for selecting institutions for site visits	1. (MET) Five proactive compliance site visits conducted.

2. Perform a risk assessment and develop a plan for reviews of compliance with grant-related policies.	2. Framework for risk assessment in place	2. (MET) Initial risk assessment of 35 grants administration policies performed; ten policies selected for compliance review.
3. Provide Internet-accessible resource information and/or tools for implementing institutional compliance programs.	3. Web site in place for grants compliance and oversight under the Office of Extramural Research	3. (MET) Internet-accessible resource information posted on enhancing institutional compliance programs.
FY 2004 1. Begin internal compliance reviews.	1. Ten policies selected for compliance reviews	1. (MET) Compliance reviews grants-administration policies were initiated.
FY 2005 1. Implement recommendations from the internal compliance reviews held in 2004. By the end of FY 2005 NIH will have developed an ongoing program for internal compliance reviews which, combined with other continuing efforts, will complete the goal of developing a strong program to ensure proper stewardship of public funding for research. FULL COST (dollars in millions) *excludes POI-3	1. Completed compliance reviews FY 04 $1	1. Performance results will be reported in February 2006. FY 05 FY 06 $1 $1

[1] Jit-Indicates that the goal is part of the President's Management Agenda.
SP-# Indicates the DHHS Strategic Plan goal to which each GPRA goal pertains.
[2] The nearly tenfold increase in the dollar volume of the performance target in FY 2002 is primarily due to a single, large, performance-based contract awarded in FY 2000.[1]

Data Limitations Affecting Performance Targeting or Reporting

NIH's scientific research outcome goals in the matrix are representative of the agency's goals. Almost all of the goals involve the scientific and/or financial contributions of more than one IC; most goals involve several ICs. This representative approach enables performance assessment of NIH's broad and complex research program. In laying the groundwork for reporting on prospectively defined targets, NIH presents linkages among inputs, processes, outputs, and outcomes in science, taking into account the following factors:

- The representative approach and specific scientific research outcome goals results in reporting on projects that are components of, but are not budget line items.

- Research outcomes are challenging to predict with a high degree of accuracy, but can be captured in many cases with milestones of progress toward the goal. Although outcomes may encompass the proposed hypothesis, unplanned results such as serendipitous discoveries and findings that narrow the avenue of the research focus (elimination discoveries) can be just as significant.

- The full value of any given research finding may not be apparent at the time of discovery, and often reaches a state of fruition after many years or in combination with other advances.

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

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

PART Efficiency Measures

YEAR	PROGRAM	EFFICIENCY MEASURE
FY05	HIVAIDS Research	*ARIS* is being improved to accommodate all budget functions and to improve the tracking and monitoring of the AIDS portfolio.
FY06	Extramural Research	Provide greater functionality and more streamlined processes in grants administration by Developing and monitoring the NIH electronic research administration (eRA).

Detailed GPRA Goal Performance Narratives by Functional Areas

Scientific Research Outcomes

NIH conducts and sponsors investigations in this country and abroad across the full range of the health research continuum, including basic research, which may be disease oriented or lead to the development and application of breakthrough technologies, observational and population-based research, behavioral research, prevention research, health services research, translational research, and clinical research. Clinical research includes research to understand both normal health and disease states, move laboratory findings into clinical interventions, and assess new treatments or compare different treatment approaches. Central to this approach is a framework that characterizes goals on the basis of risk (i.e., likelihood of attaining the goal) and time. One way of visualizing this framework is to use a three-by-three matrix.

The matrix of goals selected by NIH reflects the challenges of complex biological systems. They range across a continuum of low to medium to high risk, and they have a corresponding timeline for achievement (i.e., 1-3 years, 4-6 years, and 7-10 years, respectively). For example, the NIH portfolio includes high-risk goals that reflect the start of a scientific journey, which often means that the knowledge is limited and pathways to success are primarily unknown. Achievement of a high-risk goal in the early stages cannot be guaranteed. In contrast, NIH low-risk goals usually have a long history associated with the scientific effort, and the knowledge base has known parameters. With low-risk goals, only a few steps remain to translate the knowledge into an application that could lead to improved public health. NIH also utilizes performance goals that span the middle of the continuum. For the latter, a foundation of knowledge has been set but not extensively developed. Yet the goal is pursued because achievement is deemed probable. The elements used to determine the level of risk/ambition/difficulty include predictability of outcomes, absence of clear pathways, delivery time, and needed resources.

NIH GPRA SCIENTIFIC RESEARCH OUTCOMES (SRO) GOALS MATRIX

Risk	1-3 YEARS	4-6 YEARS	7-10 YEARS
H G, 3	**1.1** By 2005, conduct medications development using animal models and begin conducting Phase I and II trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin. **1.2** By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.	**2.2** By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans. **2.3** By 2006, develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure. **2.4** *By 2009, the Laboratory of Symptom Management will develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress, to reduce related symptom burden and to increase functional status and quality of life.*	**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 2010, develop an HIV/AIDS vaccine. **3.5** *By 2013, identify and characterize at least 2 human candidate genes that mutually influence risk for substance use disorders and risk for comorbid 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.* **3.2.1** By 2013, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1diabetes in human clinical studies.

Risk	1-3 YEARS	4-6 YEARS	7-10 YEARS
	4.1 By 2004, develop two new animal models to use in research on at least one agent of bioterror. **4.2** By 2005, develop improved animal models that best recapitulate Parkinson's disease (PD) based on emerging scientific findings of genetic or environmental influences or interactions of genes and the environment on the development of PD.	**5.1** By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens. **5.2** By 2009, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus). **5.3** By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs. **5.4** By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools. **5.5** By 2008, develop and test two new evidence-based treatment approaches for drug abuse in community settings. **5.6** *By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction.* **5.7** *By 2010, validate and compare 4 imaging methods of assessing lung cancer response to therapy.* **5.8** *By 2010, improve device(s) to measure hot flashes and test device(s) in clinical trials.* **5.9** ***By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations.***	**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. **6.3** By 2012, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach. **6.4** *By 2014, identify and characterize two molecular pathways of potential clinical significance to serve as the basis for discovering new medications for preventing and treating asthma exacerbations.*

Risk	1-3 YEARS	4-6 YEARS	7-10 YEARS
	7.1 By 2005, evaluate 10 commonly used botanicals for inhibition/induction of enzymes that metabolize drugs as a method of identifying potential botanical-drug interactions. **7.2** By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption. **7.3** By 2005, create the next generation map of the human genome, a so-called haplotype map ("HapMap"), by identifying the patterns of genetic variation across all human chromosomes.	**8.1** By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases. **8.2** By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals. **8.3** By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, nonredundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA) transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms. **8.4** By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding. **8.5** By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease. **8.6** *By 2011, extend the vision component of the National Health and Nutrition Examination Survey (NHANES) to develop stable national estimates of vision impairment.*	**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 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities. **9.3** *By 2012, create a database and analytical software that illustrates the progression of normal MRI measurement of brain development in a nationally representative sample of children in the United States.*

This continuum of scientific discovery affirms the need for a balanced portfolio with high-risk/ambitious goals as well as low-risk/probable goals and all those in between. NIH promotes ambitious goals because they hold promise to address a critical need and improve the health of the Nation. NIH recognizes that all of its goals involve some degree of uncertainty because of the risk factor inherent in the nature of scientific discovery. Through utilizing goals that span the range of the continuum, NIH is making progress toward its mission of uncovering new knowledge leading to better health for everyone.

SRO-1.1 BY 2005, CONDUCT MEDICATIONS DEVELOPMENT USING ANIMAL MODELS AND BEGIN CONDUCTING PHASE I AND II HUMAN TRIALS OF TWO POTENTIAL TREATMENTS FOR ALCOHOLISM: THE CANNABINOID ANTAGONIST RIMONABANT AND THE CORTICOTROPIN-RELEASING HORMONE ANTAGONIST ANTALARMIN.

BACKGROUND

Prevalence/Incidence

The 2002 World Health Organization report lists alcohol as the third leading risk factor for preventable, premature death in developed countries, after tobacco and hypertension.[1] In the United States, alcohol is the third leading root cause of death not attributable strictly to genetic factors, after tobacco and

[1] World Health Organization. *The World Health Report 2002: Reducing Risks, Promoting Healthy Life.* October 30, 2002. 250 pp. http://www.who.int/whr/en/.

diet/activity patterns.[2] Almost 16 million American adults are alcoholic (physically dependent on alcohol) or abuse alcohol (dysfunctional, but not dependent).[3] Children also are at risk. Almost 30 percent of 9th to 12th graders report having had five or more drinks, in a row, at least one day of the previous month.[4]

Disease Burden

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

Rationale

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Three strategies have been identified. First, NIH plans to prepare a clinical protocol to test rimonabant for its ability to reduce ethanol drinking and obtain approval to proceed. Such testing should lead to enhanced techniques for treating alcoholism. Second, NIH plans to contract for toxicology studies of antalarmin with the purpose of getting an Investigational New Drug (IND) from FDA. This toxicologic evaluation should be completed by the end of FY 2004. Third, NIH plans to design a protocol for testing antalarmin in alcoholics for relapse prevention and reduced ethanol drinking in preparation for phase I/II clinical trials to begin in 2005. Therefore, both rimonabant and antalarmin will be in clinical trials in 2005.

[2] McGinnis JM, Foege WH. Actual causes of death in the United States. JAMA. 1993 Nov 10;270(18):2207-12.
[3] SAMHSA [Substance Abuse and Mental Health Services Administration] (2003). *Overview of Findings from the 2002 National Survey on Drug Use and Health* (Office of Applied Studies, NHSDA Series H-21, DHHS Publication No. SMA 03-3774). Rockville, MD.
[4] Centers for Disease Control and Prevention. Youth 2001. http://www.cdc.gov/nccdphp/dash/yrbs/2001/youth01online.htm; Youth Risk Behavior Survey, CD-ROM Youth '99, and Youth Risk Behavior Survey, CD-ROM Youth '97.
[5] Harwood HJ, Fountain G, Livermore G. *The Economic Costs of Alcohol and Drug Abuse in the United States,* 1992. NIH Publication No. 98-4327, September 1998; updated October 1999.
[6] Smart RG, Mann RE. Alcohol and the epidemiology of liver cirrhosis. Alcohol Health Res World. 1991;16(3):217-22.

Assuring progress and successful achievement of this goal, NIH planned for toxicology studies of antalarmin with the purpose of getting an Investigational New Drug application (IND) from FDA. The next scientific step is to proceed with testing antalarmin to prevent relapse prevention in alcoholics. While scientific in nature, this step is ambitious because of the normal risks associated with any medications development program.

Prepare clinical protocol for testing rimonabant in humans.	(FY02) Two drugs have been approved for use in the US to treat alcohol addiction, with limited effectiveness				
Actual Performance: (MET) Rimonabant has been shown to reduce ethanol intake in rodent models of voluntary ethanol drinking					
Complete a toxicologic evaluation of antalarmin.	(FY03) Antalarmin and rimonabant show promise in nonhuman animal models as excellent candidates for				
Actual Performance: (MET) A toxicologic evaluation on antalarmin has been completed.					
Test antalarmin for relapse prevention in alcoholics.	(FY03) Recent studies have shown that antalarmin reduces voluntary ethanol intake in rat model of drinking			o	
Actual Performance: Performance results will be reported in February 2006.					

O Target Active • Target Met Target Extended ° Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target was met because a toxicologic evaluation of antalarmin was performed within the Clinical Center at NIH by the Intramural Antalarmin Consortium. An NIH intramural study has demonstrated that the CRH type 1 receptor antagonist antalarmin reduces neuroendocrine and behavioral responses to stress in primates (Proceedings of the National Academy of Sciences U.S.A. 97:6079, 2000), and a more recent study by others has shown that antalarmin reduces voluntary ethanol intake in a rat model of drinking. In an ongoing nonhuman primate study, antalarmin was found to reduce 5-HT1A receptor density in areas of the brain considered to be important in other drug and alcohol reward mechanisms. The toxicological evaluation of antalarmin in rats and in dogs has been completed. A pre-IND meeting was recently held to discuss progress toward obtaining an IND from FDA for a clinical trial. Once the IND is obtained, relapse prevention testing in humans can begin.

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

Implementation Strategy Advances or Other Highlights. In FY 2003, NIH proposed and achieved the target of preparing the clinical protocol for testing rimonabant in humans. The clinical protocol for testing rimonabant in humans was completed by NIH and the IRB was approved in early 2004. Subjects are now being recruited into the clinical trial of rimonabant. Clinical trial results will be forthcoming.

Efficiency. The FY 2004 target was met ahead of schedule by the NIH staff. In addition, the clinical trial of rimonabant has begun, ahead of schedule.

SRO-1.2 **BY 2006,** DEVELOP ONE OR MORE PROTOTYPES FOR A LOW-POWER, HIGHLY DIRECTIONAL HEARING AID MICROPHONE TO HELP HEARING-IMPAIRED PERSONS BETTER UNDERSTAND SPEECH IN A NOISY BACKGROUND.

BACKGROUND

Prevalence/Incidence

Approximately 28 million Americans suffer permanent hearing loss, making it one of the most prevalent disabling conditions in the United States. As Baby Boomers age, this number is expected to increase significantly. Hearing aids continue to be the only form of remediation for most people with permanent hearing loss. Only about 20% of Americans with hearing loss have hearing aids and only about half of those are satisfied with their aids. Hearing aids are not typically effective in restoring the ability to listen only to the desired speech source from among competing sound sources. This makes it difficult to hear speech in public venues such as meetings, banquets and sporting events.

Disease Burden

Sensorineural hearing loss affects people of all ages, in all segments of the population, and across all socioeconomic levels. It can interfere with an individual's physical, cognitive, behavioral, and social functions and is caused by a problem in the cochlea or the auditory nerve, the parts of the ear that help sound impulses reach the brain.

Rationale

Hearing aid users want devices that enable them to better understand speech. Two recent surveys demonstrate this desire. Poor benefit in noisy situations was listed among the top 20 reasons why hearing aid owners don't use their hearing aids. Another survey of 2,428 hearing aid owners found that improved understanding of speech in noise was among the top 10 desired changes. Of all available technologies, directional microphones have shown the most promise for addressing this problem, as demonstrated by clinical studies of individuals with hearing loss.

In spite of their promise, many engineering challenges stand in the way of achieving the full potential of directional microphones. The tremendous recent advances in signal processing have not produced marked improvements in speech intelligibility for the hearing impaired. Part of the reason for this is that processing technology has outpaced sensing technology. A primary premise of this project (SRO1.2) is that processing must be integrated with significantly improved directional microphone technology. The combined result will improve the lives of hearing-impaired individuals.

NIH-supported scientists have been studying the tiny fly *Ormia ochracea,* which has such sensitive directional hearing that it has inspired ideas for a new generation of hearing aids. The fly's ear structure, which permits ultra sensitive time coding and localization of sound, provide a model for scientists and engineers to use in developing new miniature directional microphones for hearing aids that can focus sound amplification on speech. The use of improved directional microphones in hearing aids will improve the quality of life for individuals with hearing loss who depend on hearing aids to understand spoken language.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH has identified four strategies toward developing a directional microphone prototype using improved technology. First, NIH researchers plan to design and test a device (diaphragm) that responds to sound based on the ears of the fly Ormia ochracea. Second, NIH plans to design and test the electronic circuitry needed to create a sound output from the diaphragm. Third, NIH seeks to combine the diaphragm and the electronic output circuitry into a directional microphone. Fourth, NIH plans to miniaturize the prototype directional microphone so that it is small enough to fit into a hearing aid worn behind the ear. By developing a hearing aid that mimics the sound localization abilities of the fly, NIH anticipates transferring the same sound localization abilities to hearing-impaired individuals who use hearing aids.

PERFORMANCE MEASURES	BASELINE						
Design and test a device (diaphragm) that responds to sound based on the ears of the parasitic fly *Ormia ochracea*	(FY02) Small insect model system exists and has hyperacute sound localization	•					
Actual Performance: (MET) NIH scientists successfully completed design and testing of a novel microphone diaphragm that responds to sound and is based on the ears of the parasitic fly *Ormia ochraca.*							
Design and test the electronic circuitry to create a sound output from the diaphragm.	(FY03) Sound-responsive diaphragm based on an insect model system is available		•				
FY 04 *Actual Performance:* (MET) NIH-supported scientists successfully developed the electronic output circuitry that will convert the microphone diaphragm's motion into an electronic signal.							
Combine the diaphragm and the electronic output circuitry into a directional microphone that is small enough to fit into a hearing aid. ***Adjusted to:*** Combine the diaphragm and the electronic output circuitry into a directional microphone.	(FY04) Diaphragm and electronic circuitry are available.			o			
Actual Performance: Performance results will be reported in February 2006.							
Develop a fabrication process to miniaturize the prototype directional microphone so that it will fit into a hearing aid.	(FY05) Prototype directional microphone is available				o		
Actual Performance: Actual Performance: Performance results will be reported in February 2007.							

O Target Active • Target Met Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target has been met because NIH-supported scientists successfully developed the electronic output circuitry that will convert the microphone diaphragm's motion into an electronic signal. This will result in a directional microphone that mimics the auditory system used by the parasitic fly *Ormia ochracea.* The fly's system was selected as a model for this research because its mechanically coupled ears enable its hearing to be directional and because it provides a microscale approach to developing new technology for hearing aids. The scientists used silicon microfabrication technology to make a directional microphone that is small enough to be potentially incorporated into a hearing aid. The directional microphone developed in FY 2004 will ultimately help hearing aid users to better understand speech in a noisy background, such as in a crowded room.

Implementation Strategy Advances or Other Highlights. The primary advances made during FY 2004 include the successful demonstration of an optical sensing scheme that will provide an electronic signal that is proportional to the displacement of a microphone diaphragm as it responds to sound. This system has been demonstrated using a large-scale bench-top setup on simple, non-directional microphone diaphragms. In addition, progress has been made on the fabrication and testing of a miniature version of the optical sensor electronics. The sensor

electronics utilize a semiconductor laser and photodetectors that have been integrated onto a 1.5mm by 1.5mm chip. While the current version of the sensor electronics does not yet meet the project power consumption and noise specifications, it demonstrates that significant progress has been made toward miniaturizing the system.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

Ongoing planned evaluations of the project determined that additional steps need to be taken to achieve the proposed original FY05 target. To meet the challenges of discovery research, it was determined that the FY05 target must be modified. Although the research team is hard at work and making outstanding progress towards combining the diaphragm and electronic output into a prototype directional microphone, they reported that this process may not be completed with enough time in FY05 to also start the miniaturization process. Developing a fabrication process to miniaturize the prototype microphone is a technically demanding process. Therefore, NIH proposes that the development of a fabrication process to miniaturize the prototype microphone be stated as a new target to be achieved by the end of FY06.

PART

This goal was included in the FY 2006 PART of the Extramural Research Program. See Section C.1 to review results and recommendations.

SRO-2.2 BY 2009, EVALUATE THE EFFICACY OF TWO NOVEL APPROACHES TO PREVENT WEIGHT GAIN AND/OR TREAT OBESITY IN CLINICAL TRIALS IN HUMANS.

BACKGROUND

Prevalence

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

- Approximately 65 percent of U.S. adults are overweight or obese; nearly 31 percent of U.S. adults are obese.

- About 16 percent of children and teenagers ages 6 through 19 are overweight,[2] with ominous implications for our Nation's future health.
- Racial and ethnic minority populations are disproportionately affected by obesity, particularly African American, Hispanic American, and American Indian women and children.

Disease Burden

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

NIH will explore five or more lifestyle-based approaches to obesity prevention, including behavioral or environmental interventions, in settings such as schools, communities, and homes; in addition, at least two studies will evaluate the effects on weight control of worksite interventions that include environmental components. Because maintenance of weight loss is a critical yet particularly difficult element of obesity treatment and prevention, NIH will investigate novel ways to help individuals who have intentionally lost weight to keep the weight off for at least 2 years. Specifically, the Weight Loss Maintenance Trial will compare three

different strategies for maintaining weight loss among persons who are successful in losing a targeted amount of weight over the short term. Complementing these areas of investigation relevant to lifestyle interventions will be research to evaluate the efficacy of different types of diets and physical activities. Specifically, a study is being conducted to compare the Atkins diet with a conventional weight loss diet as to long-term effects on weight and other health parameters.

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

In addition to these research efforts, in April 2003 the NIH Director Dr. Elias Zerhouni established the NIH Obesity Research Task Force as a new effort to accelerate progress in obesity research across the NIH. The Task Force is co-chaired by the Director of the National Institute of Diabetes and Digestive and Kidney Diseases and by the Acting Director of the National Heart, Lung, and Blood Institute. Currently over twenty different NIH components (Institutes, Centers, and Offices; ICs) are represented on the Task Force. A key element of the NIH Director's charge to the Task Force is the development of a Strategic Plan for NIH Obesity Research. The purpose of the Strategic Plan is to provide a guide for coordinating obesity research activities across the NIH and for enhancing the development new research efforts based on identification of areas of greatest scientific opportunity and challenge. The Strategic Plan was developed with input from external experts through interactions with NIH staff at scientific meetings; through meetings and workshops convened by NIH ICs for the purpose of obtaining research planning advice; through presentations by the co-Chairs of the Task Force to external scientific and health advocacy organizations; through solicitation of comments from scientists and leaders of voluntary and professional health advocacy organizations on a draft of the Strategic Plan; and, subsequently, through posting of a revised draft on the Web for a public comment period. The Strategic Plan for NIH Obesity Research was published in August 2004.

PERFORMANCE MEASURES	BASELINE		
Identify two new drug targets that can be used in screens for potentially therapeutic compounds in drug discovery projects or that could be evaluated for use as therapeutic agents for weight control.	(FY02) No highly effective drug therapies exist for overweight or obesity. Potential drug targets need to be identified		
FY 03	*Actual Performance:* (MET) Three molecules can be characterized and screened as targets for therapeutic compounds or evaluated as potential therapeutic agents for weight control.		

PERFORMANCE MEASURES	BASELINE					
Develop and launch at least two studies to test the effects of worksite interventions on weight control.	(FY03) No programs for weight control at the worksite have been examined in studies with valid designs to clearly evaluate if they are effective					
Actual Performance: (MET) More than two studies to test the effects of worksite interventions on weight control were developed and launched.						
Enroll and randomize 60 children with hyperinsulinimia in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children ages 6 to 12 years.	(FY03) No clinical trials have demonstrated efficacy of any medication for overweight during childhood. Pilot data suggest metformin may be of benefit for those children with hyperinsulinemia			o		
Actual Performance: Performance results will be reported in February 2006.						
Enrol and randomize 240 predominantly minority pre-adole cent girls to test the efficacy of an after school dance program in reduc ng weight gain.	(FY04) Few effective community-based interventions are available to prevent weight gain in at risk children				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The FY04 target was met by developing and launching seven studies to test the effects of worksite interventions on weight control. The NIH initiative entitled "Overweight and Obesity Control at Worksites" solicited research projects to test whether worksite environmental interventions, in combination with individual-lifestyle behavior modifications, can prevent or control overweight or obesity in adults. The interventions emphasize combinations of worksite environmental changes (e.g., fitness equipment, flex time for physical activity, changes in cafeteria and vending machine food offerings, and employee wellness counselors), and individual or family approaches (e.g., on-site diet and physical activity counseling) to obesity prevention.

Seven meritorious applications were funded in response to the initiative, a number higher than originally planned because of the unanticipated number of high quality applications received. The seven funded applications together provide a robust and broad representation of approaches to the understanding of obesity prevention that may yield effective intervention strategies. Additional funding was allocated to address this critical public health need. Through these studies, a total of 23,250 employees across various worksites including hospitals, schools, transportation, hotels, and manufacturing companies will be enrolled. The studies use body mass index (BMI) or change in body weight as the primary outcome measure. Secondary outcome measures include energy and nutrient intakes, physical activity and fitness, employee productivity, changes in worksite policies, cost effectiveness, and health care utilization.

Implementation Strategy Advances or Other Highlights. In response to the lack of studies examining therapeutic drugs to aid behavioral therapy for weight control in young children, NIH intramural scientists studying growth and obesity are conducting studies to determine whether two promising medications, metformin and orlistat, may be used for weight reduction in overweight children. In FY04, 18 children were recruited to the metformin study and 123 adolescents were recruited to the orlistat study. Preliminary findings developed over the past year from the orlistat pilot study suggest that orlistat may be effective in reducing weight and improving insulin sensitivity in some adolescents; however, more research is needed to examine the drug's effectiveness within a comprehensive behavioral intervention (McDuffie JR et al)

An NIH initiative entitled "Site Specific Approaches to Prevention or Management of Pediatric Obesity" was issued to solicit applications designed to develop and test intervention approaches for the prevention or management of overweight in children and adolescents through age 20 years.

Efficiency. Due to the large number of high-quality applications received, the target number of studies to be funded was reached and exceeded.

SRO-2.3 BY 2006, DEVELOP METHODS THAT CAN CLASSIFY AT LEAST 75% OF PROTEINS FROM SEQUENCED GENOMES ACCORDING TO EVOLUTIONARY ORIGIN AND BIOLOGICAL STRUCTURE.

BACKGROUND

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

Rationale

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

This resource will be particularly valuable to researchers such as medicinal chemists who require a synthesis of information on protein biological function, 3-D structure, and sequence conservation.

Effective antiviral drugs have been designed by targeting the conserved regions of viral proteins; for example, the virus is unable to develop resistance to these drugs because sequence changes that block drug binding also block the normal function of the protein. By describing conserved regions in detail, this proposed resource provides information that is directly useful to the medicinal chemist undertaking this research.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

Additional development of these software tools not only will improve the efficiency and quality of the data curation by the National Center for Biotechnology Information (NCBI) staff but also will provide researchers with powerful discovery tools. Distribution of these tools will also facilitate the submission of outside research results to NCBI, thus further enriching the classification resource. Using NCBI-developed software for structure-based alignments and molecular evolutionary classification, outside experts will be able to make contributions, based on their own research, in identifying homologous sites and in adding site-specific functional annotation.

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

PERFORMANCE MEASURES	BASELINE		
Develop software for making comparative alignments of protein domains according to structure and molecular evolutionary classification, and which provides functions for domain family updates.	(FY02) 256 domain families curated; software to align domains by structure and class unavailable	•	
FY 03	*Actual Performance:* (MET) Software was released which improved structure-based alignments of proteins and classification of protein domain families based on molecular evolution; software was used to annotate over 500 protein domain families.		

PERFORMANCE MEASURES	BASELINE					
Obtain annotation for a total of 1,500 protein domain families in the conserved domain database using two advanced classification methods: (1) structure-based alignment and (2) molecular evolutionary classification. Cover 35% of sequences in PubMed (the National Library of Medicine's database of biomedical research literature), extended to 70% by adding first-generation alignments.	(FY03) 800 domain families curated; 25% coverage of PubMed sequences					
Actual Performance: (MET) 1,674 domain families curated through enhancing software for molecular evolutionary classification and by bringing Conserved Domain Curator team to full strength.						
Obtain annotation for total of 2,500 protein domain families annotated by structure-based alignment and molecular evolutionary classification. Cover 45% of PubMed sequences, extended to 75% by adding first-generation alignments.	(FY04) 1,500 protein domain families curated; 35% coverage of PubMed sequences			o		
Actual Performance: Performance results will be reported in February 2006.						
Obtain annotation for total of 3,500 protein domain families annotated by structure-based alignment and molecular evolutionary classification. Cover 55% of PubMed sequences.	(FY05): 2,500 protein domain families curated; 45% coverage of PubMed sequences				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target was met by producing a total of 1,674 expertly curated protein domain family models. The target was accomplished through the following means: (1) the "CDTree" software system for molecule evolutionary classification was further developed to implement all original design goals; and (2) the Conserved Domain Database curator team was brought to its intended strength of 15 biologists, with intensive training for newly appointed team members. Together, these efforts enabled the team to produce a total of 1,674 expertly curated protein domain family models.

Implementation Strategy Advances or Other Highlights. The "CDTree" software system assists curators/users in identification of domain subfamilies with distinct biological function. The software calculates hierarchical clustering trees based on molecular sequence similarity and couples their display to taxonomic information, so curators may identify clusters corresponding to evolutionarily ancient, conserved, functions; additional useful information such as the domain architecture and search-model performance of clusters is also displayed. The software furthermore functions as an efficient data manager, allowing curators to automatically declare and record new subfamilies and/or to modify the underlying sequence/structure alignments using the "Cn3D" structure-based editing software.

While software can improve efficiency, the goals of the Conserved Domain Database project can only be met by a team of trained and expert biologists/curators. The curator team is above all responsible for identifying and citing scientific publications that describe the biological function of domain family members. By interpreting protein 3-dimensional structure, the curator team can furthermore annotate features such as enzyme active sites. Occasionally, curators must exercise judgment in interpretation of molecular data, for example in identification of possible horizontal gene transfer events or conformational flexibility. Training of the curator team by cross-checking and frequent discussion has thus been an essential component of the project.

Efficiency. During the course of 2004 software features that make domain family curation more efficient have been identified and implemented as appropriate. One example has been to streamline the "update" utilities within the "CDTree" package, which the curation team uses to identify and incorporate newly determined sequences and/or structures. Updates can now be done interactively, and optionally focused on portions of the family hierarchy selected by the curator. This, in turn, has allowed the team to concentrate on new and/or modified subfamilies. Another feature the team has researched is an algorithm for automated refinement of sequence/structure alignments. This procedure was found to improve alignments uniformly, and in some cases, significantly. These improvements contributed to the production of 1,674 curated protein domain families, a 12% increase over that projected.

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).

BACKGROUND

Prevalence/Incidence

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

- Approximately 4.5 million Americans currently have AD.
- The prevalence of the disease doubles with each 5-year increment in age in persons older than 65.
- Demographic studies suggest that if current trends hold, the annual number of incident cases of AD will begin to sharply increase around the year 2030, when all the baby boomers (born between 1946 and 1964) will be over age 65. By the year 2050, the number of Americans with AD could rise to some 13.2 million, an almost three-fold increase.

Disease Burden

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

NIH also plans to speed drug discovery and movement of promising new treatments and prevention strategies into clinical trials. It is likely that the Intervention Testing Program (ITP) will add four to five interventions for testing in each subsequent year; a Notice was issued in the NIH Guide (NOT-AG-04-003) in January 2004, soliciting proposals for additional compounds to enter the ITP. Nominations of interventions to be tested are submitted to an Access Panel, which decides whether an intervention is worth testing; the approved nominations are then prioritized by a Steering Committee. Also, neurobiologic and epidemiologic research will continue to pinpoint new targets for drug therapy, such as inflammatory processes and toxic oxidative agents known as free radicals.

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

To date, only one risk factor gene for late onset AD has been identified, despite the intense interest in determining a genetic basis for this disease. The AD genetics initiative was started to develop much-needed resources for geneticists to find the additional key late onset genes; finding and recruiting about 1000 families will be necessary to establish a data base for studies of familial inheritance of AD - just one of the objectives for this resource. Families to be recruited must have at least three members who can donate blood, and need two or more siblings *living* with AD, which is quite rare and never before attempted for AD research. In addition to blood samples, participants will participate in interviews; agree to a medical record review; be contacted for annual updates; and perhaps, undergo a medical exam, including memory testing. This is an ambitious target that will require much work to achieve by 2006. So far, an unprecedented alliance of AD Centers, researchers, and outreach personnel, aided by the Alzheimer's Association, has collected around 500 of these families, with 500 more to go.

PERFORMANCE MEASURES	BASELINE		FY 2004				
Initiate a double-blind, placebo-controlled trial of simvastatin (medication used to reduce the amount of cholesterol and certain fatty substances in the blood) to determine whether	(FY02) Earlier studies indicate lowering cholesterol levels with statins seems to have a positive impact on brain function and reduces the risk of						

PERFORMANCE MEASURES	BASELINE				
it can slow the rate of progression of AD.	AD				
Actual Performance: (MET) CLASP study was enacted to further investigate the role that cholesterol has in the pathogenesis of Alzheimer's Disease.					
Identify and implement effective strategies to facilitate drug discovery and development for AD treatment and prevention in collaboration with relevant organizations, as well as through stimulation of relevant research through Program Announcements and/or other mechanisms.	(FY03) Estimated 30 compounds are presently or will soon be tested in human AD clinical trials but additional targets are needed		•		
Actual Performance: (MET) NIH initiated a preclinical toxicology program and expanded an interventions testing program to expedite drug discovery, and identified a collaborative opportunity for pre-clinical drug development.					
Launch the Alzheimer's Disease Neuroimaging Initiative to evaluate neuroimaging modalities and techniques and other biomarkers to be used in early diagnosis, follow the progression of mild cognitive impairment (MCI) and AD, and use as potential surrogate markers for drug development and clinical trials.	(FY03) Neuroimaging technologies appear to have considerable potential for early diagnosis of MCI and AD and for measuring disease progression			o	
B *Actual Performance:* Performance results	will be reported in February 2006.				
Identify around 1,000 new late onset AD families to allow geneticists to locate additional late onset risk factor genes for AD that may lead to new targets for drug treatment, and provide a well-characterized population for more efficient clinical trials.	(FY04) The genetics initiative has identified 259 families, too few for researchers to identify the remaining risk factor genes.				o
B *Actual Performance:* Performance results	will be reported in February 2007.				

O **Target Active** **•** **Target Met** **—** **Target Extended** **X** **Target Not Met**

Summary of FY04 Performance Results

Target. The target was met. The NIH awarded a contract "Investigational New Drug Toxicology for Drugs to Treat AD and Other Aging Related Dementias" (AG4-0010) in September 2004. This preclinical drug-development program is designed to expand the potential range of drug therapies for Alzheimer's and other aging-related diseases by making toxicology resources available to a larger and more diverse group of investigators. These toxicological evaluations are required by the FDA, when requesting an Investigational New Drug (IND) designation for clinical studies.

The ITP, a multi-institutional study investigating treatments with the potential to extend lifespan and delay disease and dysfunction in mice, including AD and age-related cognitive decline and dementia, was fully established with the award of the third site in FY2004 (1U01AG022307-01). During 2004, four compounds are being tested, two of which have known anti-inflammatory action - a suspected mechanism in Alzheimer's disease.

Consensus was achieved in meetings with the Institute for the Study of Aging (ISOA) on the development of a joint program announcement (PA) for preclinical drug discovery and development. The ISOA is a biomedical venture philanthropy focused on drug discovery for cognitive aging and Alzheimer's disease; as such, it provides funding to advance early stage technology that will attract venture capitalists,

investment banking and pharmaceutical companies. This PA has an NIH set-aside of $1.5 million and highlights interest in the development of novel compounds targeted to aberrations in mechanisms of neuronal cellular communication. NIH re-issued a Request for Applications (RFA-AG-05-006) entitled "Collaborative Studies on Alzheimer and Related Diseases" in September 2004. The current release specifically targets drug discovery and development for AD treatment and prevention, as it invites applications on the relationship of exposures to agents, such as statins and hormones, to onset and progression of disease and on the value of imaging on the clinical diagnosis of AD and non-AD dementias.

Implementation Strategy Advances or Other Highlights. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a $60 million, five year public-private partnership to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. The development of the ADNI remained on target in FY2004, and award number 1U01AG024904-01 was made on September 30, 2004. The Initiative's aims are to improve diagnosis and to lessen the time and cost of clinical trials, thereby increasing the safety and efficiency of drug development.

Recent studies have reported the development of novel radiotracers that suggest it may be possible to provide quantitative imaging information on amyloid deposits in the brain. In the first human study of the amyloid-imaging tracer called Pittsburgh Compound-B (PIB), used with positron emission tomography (PET), subjects with mild AD showed marked retention of PIB in areas of the brain known to be heavily affected by AD pathology. Although further research is needed, this and other such compounds may play a major role in developing and evaluating treatments for AD targeted to amyloid deposits.

Using positron emission tomography (PET), patients with AD typically show decreased glucose metabolism, which correlates with brain activity, in specific brain regions. Other studies have shown decreases in metabolism in these same brain regions in non-symptomatic middle-aged people who are at risk for AD. In a recent study, investigators extended these findings to show that cognitively normal people who are APOE e4 carriers show the characteristic decreases in brain metabolism while in their 20s and 30s - decades before the possible onset of symptoms, and considerably earlier than previously recognized. Many experts believe that the degeneration leading to AD will be best treated as early in the course of the disease as possible, so as promising drug treatments develop, it will be even more important to identify those at risk and make early diagnoses.

A nation-wide campaign continues to recruit families in which two or more siblings are living with AD to provide a resource for geneticists looking for late-onset AD genes; such families are quite rare and need to be actively sought and recruited. This effort is being assisted by NIH-funded Alzheimer's Disease Centers and local chapters of the Alzheimer's Association.

PART

This goal was included in the FY 2006 PART of the Extramural Research Program. See Section C.1 to review results and recommendations.

SRO-3.2 BY 2010, DEVELOP ONE UNIVERSAL ANTIBIOTIC EFFECTIVE AGAINST MULTIPLE CLASSES OF BIOLOGICAL PATHOGENS.

BACKGROUND

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

Rationale

Drug-resistant infectious agents—those that are not killed or inhibited by antimicrobial drugs—are an increasingly important public health concern. Many microbes have naturally evolved resistance to the drugs commonly used to treat the diseases they cause, including those that cause tuberculosis, gonorrhea, malaria, and childhood ear infections. Antimicrobial resistance has become a factor in virtually all hospital-acquired (nosocomial) infections. Several bacterial infections soon may be untreatable due to the rise in resistant organisms. In addition to concern about the natural emergence of drug resistant microbes is the potential for bioterrorism using microbes with genetically engineered resistance to drug treatment. Better understanding of intracellular pathogens, as well as the aspects of immune response common to several types of microbial infections, could lead to new therapeutic targets such as one universal antibiotic effective against multiple classes of bacterial/biological pathogens. In addition, genomics, the science of deciphering and drawing information from the genetic code of an organism, is a powerful tool that NIH is using to understand the microbes that cause disease and design strategies to overcome them.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To accomplish the goal of developing one universal antibiotic effective against multiple classes of biological pathogens, NIH will expand its capacity for medicinal and combinatorial chemistry, library and database resources, and screening assays for use in identifying novel antimicrobial drugs. New methodologies, chemical libraries, and software tools will expand the pool of compounds that can be screened for antimicrobial properties. Expansion of NIH genomics, proteomics and bioinformatics resources will accelerate basic and applied research on microorganisms responsible for emerging and reemerging infectious diseases, including those considered potential agents of bioterrorism, and identification of gene products critical to bacterial growth and pathogenicity that may serve as targets for broad-based antimicrobials. NIH will continue to support interagency and public-private collaborative research projects to develop new antimicrobial strategies.

Through activities such as the Metagenomic Analyses of the Oral Microbiome Program, NIH plans to support genomics research to identify and characterize bacteria that cannot be grown under laboratory conditions. Such analysis may lead to the identification of new targets for antibiotics against bacterial pathogens whose involvement in infection was previously unknown, and may aid understanding of beneficial microbes. An ideal universal antibiotic would only target pathogenic microbes and not eliminate beneficial microbes. NIH also will continue to support research on bacteria found in microbial biofilms (aggregates of microbial cells on solid

surfaces), which are 10-1000 fold less sensitive to antimicrobials than those that are not growing as biofilms. New and ongoing biofilm initiatives will aid understanding of the resistance of biofilm-associated bacteria to antimicrobials and explore strategies to prevent, diagnose and treat diseases caused by biofilm-associated bacteria.

PERFORMANCE MEASURES	BASELINE					
Identify one molecule with a common role in bacterial and viral infections that may serve as a target for broad-spectrum antimicrobial drug development.	(FY02) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule with a common role in both bacteria and viruses	•				
Actual Performance: (MET) Two different molecules with a common role in different classes of microbes were identified.						
Identify one molecule or mechanism that is shared by a class or across different classes of microbes that may serve as a target for broad-spectrum antimicrobial drug development.	(FY03) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes		•			
Actual Performance: (MET) A drug/metabolite transporter molecule from the malarial parasite *Plasmodium falciparum,* that is similar to transporter molecules in other protozoa, may serve as a target for drugs to increase responsiveness to drug therapies.						
Develop a lead compound for one of the molecules or mechanisms identified as a potential target for broad spectrum antimicrobial drug development. ***Adjusted to:*** Develop a set of screening tools that will help evaluate potential compounds/classes of compounds for activity against multiple bacterial and viral infections.	(FY04) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes			o		
Actual Performance: Performance results will be reported in February 2006.						
Use screening tools to evaluate potential compounds or classes of compounds for activity against multiple classes of infectious diseases.	(FY04) Screening tools for evaluation of potential compounds/classes of compounds for activity against multiple bacterial and viral infections developed				o	
Actual Performance: Performance results will be reported in February 2007.						

o	**Target Active**	•	**Target Met**	**Target Extended**	X	***Target Not Met***

Summary of FY04 Performance Results

Target. The FY 2004 target was met. A mechanism was uncovered for how a transporter molecule from *Plasmodium falciparum,* which is similar to transporters found in other protozoan species, mediates susceptibility and resistance to several diverse antiparasitic drugs. This molecule, called PfCRT, is a transmembrane transporter protein that, when mutated, promotes the transport of some antiparasitic drugs out of the digestive vacuole of the parasite, which is the site of important detoxification processes that maintain viability of the parasite. These PfCRT mutations are responsible for resistance to drugs that must remain in the digestive vacuole in order to kill the parasite. A study conducted by NIH-supported researchers showed that mutations in the PfCRT transporter can also determine responsiveness of *Plasmodium falciparum* to other structurally diverse antimalarial drugs. They also showed that PfCRT-mediated drug resistance could be overridden when another drug that bound a different site on the protein was present. This suggests that different sites on the *P. falciparum* PfCRT protein may be potential

targets for drugs that could increase susceptibility of parasites to drug therapies, including those to which they had previously shown resistance.

Implementation Strategy Advances or Other Highlights. On August 16-17, 2004, NIH hosted a Summit on the State of Anti-Infective Development that brought together leaders from government and the pharmaceutical industry to assess the current state of antimicrobial development. A major focus of the meeting was to identify perceived barriers to development of new anti-infectives and to determine opportunities to help overcome those barriers through collaborations between NIH and the public and private sector. This meeting furthered the planned implementation strategy to continue to seek ways to collaborate with private industry partners on discovery and development of antimicrobials.

In FY 2004, NIH continued to support the *In Vitro* Antiviral Screening Program, which has screened compounds using the tools and resources such as new methodologies, chemical libraries, and software tools.

In FY 2004, NIH implemented significant expansion of microbial genomics, proteomics and bioinformatics capabilities that may be used by the research community to advance efforts to identify new antimicrobial drugs. These accomplishments include establishment of eight new NIH contracts for Bioinformatic Resource Centers and seven for Biodefense Proteomics Research Programs, and expansion of the Pathogen Functional Genomics Resource Center. These resources will aid understanding of the pathogen and/or host cell genomes and proteomes for the discovery and identification of novel targets for the next generation of drugs, vaccines, and diagnostics.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

The NIH supports research to facilitate the discovery and evaluation of drugs for infectious diseases. This research is supported at all three phases of the process: discovery, preclinical evaluation, and clinical evaluation in human trials. Much of the relevant research responsive to this goal and supported by the NIH is currently at the discovery stage, and there are multiple steps in this phase alone. In that regard, one important step that needs to be added to the performance targets section is the development of adequate tools to assess the activity of any potentially viable compounds against classes of microbes. These drug screening tools are an imperative part of the drug development process because they allow for proof of principle of biological activity by first *in vitro* and *in vivo* assessment of compound versus microbe interaction in an appropriate assay. Anticipated assays include standardized *in vitro* antimicrobial susceptibility testing and *in vivo* evaluations of the compound in a small animal infection model. These steps must be passed before pre-clinical toxicity and subsequent clinical tests are to be considered. These revised targets broaden NIH's capability to assess potential compounds and will enhance the possibility of identifying promising leads. Therefore, NIH proposes a modification to the FY 2005 performance target to more fully depict the necessary steps in the scientific discovery process. The original FY 2005 target would indicate achievement of the goal which is not feasible in the indicated time frame. This modification will not affect the ultimate endpoint, which is to develop a universal antibiotic.

SRO-3.3 BY 2013, DETERMINE THE EFFICACY OF USING SALIVARY DIAGNOSTICS TO MONITOR HEALTH AND DIAGNOSE AT LEAST ONE SYSTEMIC DISEASE.

BACKGROUND

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH plans to implement research projects that will integrate technologies to efficiently and simultaneously analyze key components of salivary secretions. Conventional and emerging technologies will be used to analyze salivary secretions from the parotid, submandibular, and sublingual glands. Bioinformatics and biocomputational tools will catalogue and annotate salivary components, resulting in a fully developed salivary proteome knowledge base. It is anticipated that a multidisciplinary team will ultimately produce a "periodic table" of salivary secretory proteins. Furthermore, NIH plans to develop integrated microsystems to detect disease-associated biomarkers in human saliva. Taken together, this information will help improve understanding of how salivary components change in the presence of disease or disorder.

PERFORMANCE MEASURES			FY 2004	FY	FY	FY	FY 200S
Implement at least five research projects directed at developing integrated technologies for the efficient and simultaneous detection of key molecules in human saliva.	(FY02) No integrated technologies to quickly and efficiently measure multiple substances in saliva						
Actual Performance: (MET) Seven research projects implemented to develop technology aimed at human salivary diagnostics.							
Implement research projects directed at identifying and cataloging saliva proteomes. Identification of salivary proteomes will help scientists detect changes in saliva that are associated with specific diseases or conditions.	(FY03) Technology available to help identify salivary proteomes		•				

PERFORMANCE MEASURES	BASELINE					
	Actual Performance: (MET) Three research projects implemented to identify and catalog salivary proteomes.					
Develop electronic microfluidic assay systems (e.g., microchip-based systems that are replacing large and costly instruments) that can quantify C-reactive protein (a biomarker for cardiovascular disease) in saliva.	(FY03) Systems to quantify C-reactive protein in saliva have not yet been developed			o		
	Actual Performance: Performance results will be reported in February 2006.					
Finalize the fabrication of a portable handheld diagnostic device that can detect associated with oral and/or systemic diseases, and develop methods for its quality assurance and standardization.	(FY04) Currently the individual components needed for a portable handheld diagnostic device are under fabrication and validation				o	
FY 06	*Actual Performance:* Performance results will be reported in February 2007.					

O Target Active • Target Met — Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The target was met as three research projects designed to identify and catalog human salivary proteomes were implemented in FY 2004 as cooperative agreements. These projects are directed at identifying salivary proteins from parotid, submandibular, and sublingual salivary fluids. Researchers are using high throughput mass spectrometry techniques to define the primary structure of salivary proteins. Multidisciplinary research teams have been formed, bringing together different scientific expertise at universities across the country to participate in this effort.

Implementation Strategy Advances or Other Highlights. The implementation of efforts to identify and catalog the salivary proteome is complementary to the Salivary-Based Diagnostic Technologies program. The projects that NIH has implemented this year are specifically designed to help identify all protein components in human saliva, as well as their natural variants and complexes.

Through the Salivary-Based Diagnostic Technologies program, NIH is building towards a rapid, efficient salivary diagnostics system by developing integrated technologies to efficiently and simultaneously analyze substances found in human saliva. Working together, scientists and engineers have made substantial progress towards developing a fully integrated handheld device for measuring different hormonal levels in saliva. This device is designed to be fully portable as well as affordable. It can process and analyze saliva samples quickly and efficiently. Applications for new salivary diagnostics procedures are also being developed. For example, a group of scientists are using microchip technologies, together with a new miniaturized detection system, to measure Epithelial Growth Factor Receptor (EGFR) and interleukin levels in saliva as a way of monitoring periodontal disease and perhaps oral cancer. In addition, two groups of investigators are developing sensor arrays for the efficient and simultaneous analysis of different components in saliva. The initial work of the first group has focused on renal and asthmatic patients. The second group is developing a fully integrated system for measuring C-reactive protein (CRP) in saliva. CRP is an important biomarker for cardiovascular disease, this technology could help doctors and patients routinely assess cardiovascular risks before symptoms appear.

SRO-3.4 BY 2010, DEVELOP AN HIV/AIDS VACCINE.

BACKGROUND

Prevalence/Incidence

The HIV/AIDS epidemic has killed more than 22 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide. At the end of 2003, an estimated 37 million adults and 2.5 million children younger than 15 years of age[i] were living with HIV/AIDS. In addition, over 3 million people died from AIDS in 2003, and 5 million people were newly infected with HIV, of which 700,000 were children. A recent UNAIDS report stated, "Beyond Sub-Saharan Africa more recent epidemics continue to grow in China, Indonesia, Papua New Guinea, Viet Nam, several Central Asian Republics, the Baltic States, and North Africa". In the United States, an estimated 886,575 people are living with HIV/AIDS. Although in the United States new infections have remained relatively stable at approximately 40,000 per year, HIV infections are continuing to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people older than 50 years of age.

Disease Burden

The impact of AIDS on developing nations and many countries of the former Soviet Union is profound. Lost productivity and profitability, the cost of sickness and death benefits, and the decline in a skilled workforce in the developing world will have economic effects worldwide. AIDS is affecting the military capabilities of some countries, as well as international peacekeeping forces. In Africa, the epicenter of the pandemic, AIDS is sabotaging economic development, leading to famine and massive social breakdown and creating a generation of orphans.

Rationale

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

NIH is designing and testing new vaccine candidates based on research findings on the structural components of HIV and on studies of immune responses in small animals and nonhuman primates (NHPs). Vaccine candidates also are being constructed based on isolates from many regions of the world, and several research groups are exploring mixtures of viral components from different isolates and clades. NIH is testing new vaccine strategies using different adjuvants, immune modulators, and delivery components to optimize the immune responses that result. NIH will fund additional basic research to better understand why some individuals exposed to HIV resist infection or are able to control disease progression.

The initial goal of developing an HIV/AIDS vaccine by 2007 was based in part on the anticipated success of AIDSVAX, a candidate vaccine tested by VaxGen, Inc. However, the results of this Phase III trial showed that, overall, AIDSVAX did not prevent infection. The 2007 goal was also based on the anticipation that a modified canarypox vector (ALVAC vCP1452 from Aventis), designed for use in the Western hemisphere, Europe and Australia, would meet immune response goals in a Phase II trial initiated in 2001. When that product failed to meet its target, the decision not to move into Phase III testing was made. Additionally, while products in earlier stages of testing in the pipeline might prove to be more effective, these products are unlikely to complete testing by 2007. With these issues in mind, the goal has been changed to 2010, which is when results from the next 1 to 2 efficacy trials will be available.

In 2003, NIH, in collaboration with the Department of Defense (DoD) and the Royal Thai Government, initiated a Phase III trial of a recombinant canarypox vector vaccine candidate (ALVAC - vCP1521 from Aventis) combined with AIDSVAX B/E designed for use in Southeast Asia. In striving to meet the goal, a significant investment of NIH resources has been made in product development. This will ensure that there is a vibrant pipeline to support HIV vaccine development efforts. Significant additional resources will be required to support large-scale manufacture of new candidate vaccines and to conduct large efficacy trials to meet the 2010 goal.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH has expanded and will continue to expand breeding and increase output of specific pathogen-free macaques at three or more primate centers for the preclinical testing of vaccine candidates. In addition, NIH will produce and test at least one new virus stock for challenge of vaccinated animals.

Ten new candidate vaccines entered NIH-funded Phase I trials in the 18 months prior to May 2004; eight of which were advanced in whole or in part with NIH funding. An estimated 4 to 8 new candidate vaccines are slated to enter Phase I trials in the next 2 years; they will be produced (according to Good Manufacturing Practices) and tested preclinically with NIH funding. NIH also will prepare for and initiate 2 Phase II trials of new HIV vaccine candidates in the next two years. NIH currently is preparing for a Phase IIb trial of a third generation vaccine candidate. This study is designed to determine if the vaccine candidate is effective in either preventing HIV infection or in delaying disease progress or diminishing the course of HIV disease in those who do become infected as a result of high risk behavior.

To prepare for future large-scale clinical trials, NIH will compile seroincidence data from 2 to 3 three sites that focus on populations of minorities in the United States, or on heterosexual transmission in either domestic or international settings, and develop key regional or national laboratories capable of evaluating the safety of candidate vaccines in resource-poor settings. These capacity-building efforts will include providing the necessary training of personnel and developing quality assurance/quality control programs for these activities.

PART TARGETS FY 2005

NIH continues to make progress toward achieving the HIV/AIDS Research Program goal: to develop an HIV/AIDS vaccine by 2010. The FY 2005 PART targets for achieving this goal are as follows:1) Expand breeding of non-human primates: 3 centers; 2) Test 1 new virus stock; 3) Test 2 vaccine candidates in animals; 4) Phase I human trials: 1 vaccine candidate; 5) Seroincidence data: 3 sites; 6) Evaluate vaccine safety: 2labs; 7) Initiate 4 phases 1 and II vaccine trials; 8) Produce candidate vaccine for phase III trials.

PERFORMANCE MEASURES	BASELINE		
Design and develop new or improved vaccine strategies and delivery/production technologies.	(FY02) Existing DNA and viral-vector vaccines strategies require further evaluation	•	
iFY 1 [03 *Actual Performance:* (MET) Four newly identified vaccine strategies increased scientific knowledge of how AIDS causes disease and the immune response to it.			

Initiate one to two multinational trials in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.	(FY03) HIV Vaccine Trials Network currently supports clinical trials at 12 international sites					
FY 04	*Actual Performance:* (MET) Two multinational trials initiated in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.					
Initiate four new Phase I or II trials of new or improved concepts and designs and expand capacity to conduct clinical trials in three international sites.	(FY04) NIH has conducted 68 Phase I and Phase II HIV vaccine trials to date			o		
	Actual Performance: Performance results will be reported in February 2006.					
Initiate 1 new Phase IIb trial to determine if a third generation vaccine candidate has efficacy.	(FY04) NIH is conducting a Phase III trial of a second generation vaccine (canarypox) in Thailand				o	
	Actual Performance: Performance results will be reported in February 2007.					

O Target Active • Target Met Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target was met because two multinational trials, in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries, were initiated. Briefly, NIH working with the HIV Vaccine Trials Network (HVTN) and in collaboration with the U.S. Army Medical Research and Materiel Command (USAMRMC) initiated two HIV vaccine trials in international settings and particularly, in resource poor developing countries.

As part of its collaborative agreement with the DoD, NIH initiated a Phase III trial of Aventis Pasteur live recombinant ALVAC-HVI (vCP1521) and VaxGen gp120 B/E (AIDSVAX B/E) in Thailand. The study, known as RV144, began vaccinating HIV-uninfected adults in October 2003, and as of September 19, 2004, had enrolled 5,587 individuals out of the 9,348 who had been screened. The rationale for combining vaccine is to achieve induction of a range of immune responses that includes cell-mediated immunity (CMI) and antibody-mediated immunity (AMI).

In FY 2004, the HVTN initiated a Phase I trial (HVTN 040) in the United States and Durban, South Africa. HVTN 040 is testing the safety and immunogenecity of a novel Alphavirus replicon HIV subtype C *gag* vaccine (AVX101, Alphavax, Inc.) in healthy HIV-1 uninfected adults. Enrollment in South Africa was initiated in November 2003, (U.S. participants were enrolled prior to this) and vaccinations were completed by September 30, 2004. To date, the product appears to be well-tolerated with a favorable safety profile. Preliminary analysis of immunogenicity data of U.S. participants is already underway.

Implementation Strategy Advances or Other Highlights. HIV vaccine testing in animal models is an important step in determining whether or not a candidate vaccine will move into human clinical trials. At present, NIH is supporting 20 active NHP studies, involving over 400 macaques. Additionally, ten studies were completed during FY 2004. Also in FY 2004, NIAID titrated a challenge stock (E660) in preparation for its use in future vaccine trials involving macaques and a second SHIV challenge stock (SHIV SF-162) was produced and titrated. The production of a third challenge stock is currently underway.

The majority of NIH-supported clinical trials of preventive HIV vaccines are carried out in the HVTN. Its global capacity allows for rapid expansion as vaccine candidates enter the pipeline for testing and

development and for carrying out larger scale studies of suitable vaccines. Clinical trial research capacity has also been expanded by providing research training support for international HVTN sites through the AIDS International Training and Research Program.

In addition, the NIH's Adolescent Trials Network is building a primary prevention infrastructure. This program, Connect to Protect, will be able to support future vaccine research among adolescents in racial and ethnic minority communities in the United States. Through the Partnership for AIDS Vaccine Evaluation, the NIH has led efforts to improve coordination and collaboration among all federal agencies and their partners engaged in HIV vaccine research. Notable among these efforts is progress toward the standardization of key laboratory assays.

Nine candidate vaccines for which NIH supported the Good Manufacturing Practices (GMP) manufacture and preclinical testing entered clinical trials in FY 2004, either in the HVTN, NIH's Vaccine Research Center (VRC), or through the HIV Vaccine Design and Development Teams. Human clinical trials that were initiated or completed during FY 2004 include: two trials initiated as part of the cooperative interagency agreement with USAMRMC (one Phase III trial and one Phase I trial); nine clinical trials initiated or continued through the HVTN, the VRC and the HIV Vaccine Design and Development Teams (HVDDT); seven vaccine clinical trials completed by the HVTN and the HIV Vaccine Design and Development Teams (Phase I and II). Several of these trials are being conducted at non-U.S. sites including: Botswana, South Africa, Peru, Brazil, Haiti and Australia.

The NIH HVTN Laboratory Program (LP) consists of three core laboratories that support all ongoing HVTN trials, a regional laboratory in South Africa and a network of six collaborating laboratories in the United States. During the past year, a number of steps have been taken to further the development of laboratories capable of evaluating the safety of candidate vaccines in resource-poor setting and ensure high quality assurance and quality control programs. Four of the laboratories performing end-point immunological assays for vaccine trials adopted and complied with Good Laboratory Practices and a state-of-the art laboratory quality assurance program was developed to address clinical sites/safety labs and end-point monitoring labs.

In order to accelerate the process of initiating new vaccine production projects and expand the vaccine development capabilities, a Master Contract for Preclinical Development was competitively awarded in FY 2004. The contractor has the ability, either in house or through subcontracts, to produce vaccines as well as microbicides, carry out preclinical safety and immunogenicity testing, and assemble and submit documentation to the Food and Drug Administration for Investigational New Drug approval.

PART PROGRESS ON KEY PERFORMANCE MEASURES FY 2005

NIH continues to make progress toward achieving the FY 2005 PART targets for the HIV/AIDS Research Program goal: to develop an HIV/AIDS vaccine by 2010. NIH-sponsored basic research is continuing to provide crucial information necessary for the design and development of new and better vaccine candidates.

Progress has been made in meeting the PART annual targets FY 2005 : 1) Breeding capacity for non-human primates (rhesus and pigtailed macaques) has been expanded at 3 centers and offspring will be born in the spring of 2005; 2) Several stocks of virus for animal challenge studies have been produced, and one or more will be selected and assessed in animals during FY 2005; 3) Studies of 2 new viral vectors as well as other candidate HIV vaccines are being tested in preclinical studies in animals that will continue for 1-2 years; 4) Two vaccine candidates are being produced under GMP guidelines; 5) Seroincidence data are being collected at sites in Africa, China and the Caribbean; 6) Safety and toxicity testing is ongoing for 2 vaccine candidates that are scheduled to enter trials in 2005 or 2006; 7) Three new vaccine candidates are scheduled to start Phase I trials in early 2005, and one or more new candidates

also should start Phase I trials by the end of the summer. In addition, a large phase IIb trial will be initiated in 2005 in collaboration with Merck; 8) Production of the VRC products for a large Phase IIb efficacy trial is ongoing in preparation for a larger Phase III trial.

SRO-3.2.1 BY 2013, DEMONSTRATE THE FEASIBILITY OF ISLET TRANSPLANTATION IN COMBINATION WITH IMMUNE TOLERANCE INDUCTION FOR THE TREATMENT OF TYPE 1 DIABETES IN HUMAN CLINICAL STUDIES.

BACKGROUND

Prevalence/Incidence

Type 1 diabetes is an autoimmune disease in which the immune system attacks and destroys the insulin-producing islet cells of the pancreas. Approximately 120,000 people with type 1 diabetes are younger than 20 years of age, making this one of the most common chronic diseases of childhood. 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, lead to severe and life-threatening complications, including heart disease, blindness, peripheral neuropathy, foot ulcers, and kidney failure. Treatment requires insulin administration through multiple daily insulin injections or use of an insulin pump and careful attention to diet and activity; blood sugar levels must be measured several times a day by finger pricks. However, even with careful attention to insulin dosing, the most medically compliant patients are rarely able to maintain "tight" or physiologic control of their blood sugar. As a result, existing treatments can delay and diminish, but not prevent, many of the complications of diabetes. Even with careful attention to control of blood sugar, type 1 diabetes results in a reduction in quality of life and leads to premature death.

Rationale

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

The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated diseases, including autoimmune disorders such as type 1 diabetes. Research is under way to develop selective, short-term, durable therapies that will eliminate pathogenic immune responses, such as graft rejection and autoimmune injury, while preserving protective immunity. Tolerance induction holds great potential for improving the quality of life of individuals afflicted by type 1 diabetes and other immune-mediated diseases. If successful, tolerance induction would (1) enable lifelong, rejection-free maintenance of islet cells and (2) eliminate ongoing autoimmune injury to transplanted islets without the many adverse effects of broadly immunosuppressive drugs.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

PERFORMANCE MEASURES	BASELINE		FY 2004				
Recruit 12 participants for a Phase I trial to evaluate the safety of anti-CD52 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	(FY02) First trial of anti-CD52 to promote tolerance		X				
1 *Actual Performance:* (NOT MET) Anti-CD52 was determined to be unsafe by a non-NIH supported trial of the agent in the target population. Therefore, the opening of the NIH-supported trial was cancelled.							
Recruit 8-12 participants for a Phase I trial to evaluate the safety of anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	(FY03) First trial of anti-CD3 to promote tolerance			-	-	-	
1 *Actual Performance:* (EXT) Protocol for Phase I trial to evaluate anti-CD3 antibody is on hold, pending submission to and review of safety information by the FDA. Target completion is expected in FY 2007 if trial opens in FY 2005.							
Establish the baseline success rate for islet transplantation, which may impact U.S. Food and Drug Administration (FDA) and Medicare standards of care for islet transplantation. ***Adjusted to:*** Submit response to FDA addressing safety concerns about anti-CD3 antibody.	(FY03) An international multi-center trial of islet transplantation using the Edmonton protocol in patients with type 1 diabetes met the target enrollment of 36 subjects. ***Adjusted to:*** First trial of anti-CD3 to promote tolerance.						

PERFORMANCE MEASURES	BASELINE					
Actual Performance: Performance results will be reported in February 2006.						
Analyze data from phase 1 trial(s) and initiate development of efficacy trial(s), if appropriate. ***Adjusted to:*** Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	(FY04) Phase 1 trial(s) to promote tolerance induction are in protocol development ***Adjusted to:*** First trial of anti-CD3 to promote tolerance.				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met — Target Extended X Target Not Met

Summary of FY 2004 Performance Results

Target. The FY 2003 performance target was extended to FY 2004. At the end of FY 2003, the protocol for a Phase I trial to evaluate the safety of anti-CD52 antibody to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs had been approved by Health Canada (FDA counterpart), but it was pending approval at the participating clinical sites before enrollment could be initiated. The performance target was extended to February 2004 since site approval was expected by January 2004. In January 2004, the NIH cancelled the Phase I trial of anti-CD52 antibody because of unexpected safety issues identified in a separate, non-NIH supported trial of this agent in the target population (personal communication from investigator).

The FDA has placed a clinical hold on the further evaluation of anti-CD3 antibody in clinical trials pending its review of additional safety information on this agent. The NIH clinical hold response to the FDA will be submitted during the first quarter of FY 2005 with a response from the FDA anticipated in the second quarter of FY 2005. It is anticipated that enrollment will be initiated within six months after the FDA has released the clinical hold on this agent.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

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. However, research in this area is high risk. The first agent that was to be tested in a Phase I trial, anti-CD52 antibody, was determined to be an unsafe product in the target population. The other agent under investigation, anti-CD3 antibody, is on clinical hold by the FDA. Currently, other biologic agents in development are not ready to move into Phase I clinical trials. NIH expects that the FDA will remove the clinical hold on anti-CD3 antibody and anticipates initiating enrollment into the Phase I trial of it within six months after the hold is released. The extension of the completion date to FY 2013 from the original completion date of 2007 for the GPRA goal *By 2007, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies* is necessary due to: the time required to enroll participants (two years), the length of the trial (five years), and the time necessary to analyze data and publish the results (one year). Furthermore, the FY 2005 and FY 2006 performance targets were changed because their successful completion was dependant on the opening of the anti-CD52 and anti-CD3 trials.

SRO-4.1 **BY 2004,** DEVELOP TWO NEW ANIMAL MODELS TO USE IN RESEARCH ON AT LEAST ONE AGENT OF BIOTERROR.

BACKGROUND

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

Rationale

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

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

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

be done in small animals, which can be obtained and maintained more easily and at lower cost, prior to testing in NHP models.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To accomplish the goal of developing two new animal models to use in research on at least one agent of bioterror, NIH launched the new initiative *In Vitro* and Animal Models for Emerging Diseases and Biodefense to expand on previous efforts to develop animal models of viral diseases. This initiative supports the development, validation, and use of small-animal and NHP models to screen and test the efficacy of therapeutics, diagnostics, and vaccines for both viral and bacterial pathogens, including emerging infectious agents and Bioterrorism Category A-C agents. New small-animal and NHP models will alleviate the bottleneck caused by the shortage of validated models and accelerate the rate of product development. Awards for the *In Vitro* and Animal Model contract initiative were made in late FY 2003 and early FY 2004, and task order awards are made on a continuing basis.

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

In collaboration with FDA and USAMRIID, NIH is supporting the development, standardization, and transfer of a pneumonic plague animal model to a central repository. NHP models will be used to screen five licensed antibiotics for efficacy in treating pneumonic plague, and the data obtained are being submitted to a pre-IND FDA file which pharmaceutical companies can cross-reference in their IND applications to sponsor new label indications.

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

NIH will also employ a coordinated network of contracts and an Interagency Agreement with USAMRIID to further refine the nonhuman primate model for monkeypox. This model is planned for a critical study in partial fulfillment of the FDA Animal Rule (21 CFR 601.91) for licensure of the Modified Vaccinia Ankara (MVA) smallpox vaccine as an alternative smallpox vaccine for those who are at risk of complications from vaccination with Dryvax.

PERFORMANCE MEASURES	BASELINE		FY 2004	
Conduct validation studies of new monkey models of smallpox by employing them in testing new smallpox vaccines and therapies.	(FY02) Previous non-human primate models of smallpox/orthopox diseases inadequately modeled the progression of human smallpox disease			
FY 2003	*Actual Performance:* (MET) Human variola and models were tested for protection against disease when administered Modified Ankara (MVA) or Dryvax smallpox vaccines.			
Expand by 25% the animal model resources available for use by the research community and for licensing products under the FDA Animal Efficacy Rule.	(FY03) 8 animal models available			

Actual Performance: (MET) Two new models of viral hemorrhagic fevers and encephlitides, a model of flea-borne plague transmission, and two models of West Nile virus (Category B agent) have been developed.

O Target Active • Target Met Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target was met and exceeded because a total of five animal models have been developed, three more than had been planned. Briefly, two new animal models of viral hemorrhagic fevers and encephalitides, a model of flea-borne plague transmission, and two models of West Nile virus (Category B agent) have been developed. More specifically, the models for Category A agents include: a mouse model of bunyaviruses (e.g., Hantavirus and Rift Valley Fever Virus); a hamster model of arenaviruses (e.g., Lassa Fever Virus, and Junin Virus); and a flea-to-mouse plague transmission model of flea-borne plague. Additionally, a mouse and a hamster model of West Nile Virus, a Category B agent, were developed. In total, these accomplishments exceeded the original goal to develop two new animal models for at least one agent of bioterror by 2004. Through achievement of both the FY 2003 and FY 2004 targets, GPRA goal SRO-4.1 has been accomplished. Development of these new animal models, several of which were ahead of schedule, will allow accelerated research toward new diagnostics, vaccines, and therapies for biodefense.

Implementation Strategy Advances or Other Highlights. In FY 2004, the NIH continued to support research programs that seek to develop and make available appropriately validated animal models for biodefense. In FY 2004, NIH expanded the *In Vitro* Animal Models for Emerging Infectious Diseases and Biodefense initiative. The goal of this initiative is to provide a range of animal models, including nonhuman primate models, for preclinical testing of new therapies and vaccines. As a result, additional animal models are being developed. Specifically, the program was expanded to include models of poxviruses and the SARS coronavirus, and for the testing of neutralizing agents for inhalational anthrax. The contracts supported under this RFP cover safety, toxicology, and pharmaceutical testing in small and large animals, including the capability for conducting challenge studies.

In FY 2004, under a coordinated network of contracts, NIH continued to support the development of animal models and screening of compounds for activity against orthopoxviruses (murine models of vaccinia, cowpox, and ectromelia), respiratory viruses (murine models of influenza A and B), and viral hemorrhagic fevers and encephalitides (arenaviruses, bunyaviruses, filoviruses).

Efficiency. NIH has met and exceeded the FY 2004 target by developing five animal models, three more than had been planned. Development of these new animal models, several ahead of schedule, will allow accelerated research toward new diagnostics, vaccines, and therapies for biodefense.

SRO-4.2 BY 2005, DEVELOP IMPROVED ANIMAL MODELS THAT BEST RECAPITULATE PARKINSON'S DISEASE (PD) BASED ON EMERGING SCIENTIFIC FINDINGS OF GENETIC OR ENVIRONMENTAL INFLUENCES OR INTERACTIONS OF GENES AND THE ENVIRONMENT ON THE DEVELOPMENT OF PD.

BACKGROUND

Prevalence/Incidence

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

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

Disease Burden

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

Rationale

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

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

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

Planned Implementation Strategies

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

NIH also plans to develop a rotenone mouse model that mimics aspects of human PD. The model will be characterized for resulting neuropathological, behavioral, and chemical effects and the protocol will be made available to PD research community. If preliminary studies in normal mice reveal a reduction in dopamine levels after rotenone exposure, then NIH will combine it with one or more genes implicated in PD (e.g., alpha-synuclein, parkin) to study gene-environment interactions.

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

PERFORMANCE MEASURES	BASELINE				
Establish a mouse model repository at a Morris K. Udall Center of Excellence for Parkinson's Disease Research to house PD genetic models and make them available to the PD research community.	(FY02) No repository with this specific housing and distribution capacity exists for PD research	•			
Actual Performance: (MET) Mouse model repository to house PD genetic models established.					
Determine if slowing the metabolism of rotenone through cytochrome P-450 inhibition facilitates creation of a mouse model for PD. *Adjusted to:* Conduct dose response studies of chronic rotenone administration in normal mice and assess resulting changes in striatal dopamine levels and the number of dopamine neurons in substantia nigra.	(FY03) Cytochrome P-450 accelerates rotenone metabolism in mice so that the PD phenotype cannot be shown		•		
Actual Performance: (MET) Provided proof of concept in mouse model by administering rotenone and achieving 30-40% depletion of dopamine in striatal terminal fields with clear evidence of degenerating neurons.					
Combine the mouse model with at least one genetic model of PD and assess its interaction with rotenone.	(FY03) A rotenone mouse model is not yet available			o	
Actual Performance: Performance results will be reported in February 2006.					

O Target Active • Target Met Target Extended ° Target Not Met

Summary of FY04 Performance Results

Target. The target was met since the "proof of concept" for the mouse rotenone model was successfully completed. Dose response studies of chronic rotenone administration showed that when rotenone was administered at the limit of solubility (10mg/kg) for a maximum duration of time (30 days), a 30%-40% depletion of dopamine in striatal terminal fields was observed. Also, there was clear evidence of degenerating neurons.

With this protocol there was little or no loss of dopamine cells (located in substantia nigra). This is not unexpected, as terminal degeneration often precedes cell body loss. Thus, a testing protocol has been created that is on the threshold of producing frank degeneration. The next step will be to test this protocol in a genetically susceptible transgenic mouse strain. This model will offer a way to use a variety of genetically sensitive mice to determine critical gene-environment trigger for PD development.

Implementation Strategy Advances or Other Highlights. With the dose response protocol, there was little or no loss of dopamine cells (located in substantia nigra). This is not unexpected, as terminal degeneration often precedes cell body loss. Thus, a testing protocol has been created that is on the threshold of producing frank degeneration.

Other modifications to the rotenone protocol are also being examined. One that looks promising is feeding rodents a vitamin E-deficient diet. This regimen appears to greatly increase the extent of rotenone-induced lesions in the model studied (normal, non-transgenic rats).

Although rodents are an inexpensive and easy model to use, primates remain the animals most relevant for duplicating human responses. For some years the research community has been able to duplicate in monkeys the rigidity and loss of muscle control found in human PD by administering the synthetic chemical, MPTP. This model is limited, though, because it does not create the defining brain lesion seen in human PD, called Lewy bodies. NIEHS-supported scientists, in pilot tests, have found that chronic administration of rotenone in monkeys leads to the appearance of intracellular structures in the brain that resemble Lewy bodies. If this finding is validated in a larger sample, it will provide a more relevant model for testing therapeutic interventions, as well as gene-environment connections for PD.

Other projects also target development of improved animal models. Many of these studies involve the manipulation of genes that have been linked to the development of PD in humans. For example, following the discovery of the role of mutations in the parkin gene with a rare early-onset form of PD, grants were awarded that involved creating fruit fly and mouse strains with parkin mutations. Already, these critical animal models of PD are providing insights into the complex role that the parkin gene may play in the development of the disease in humans.

Also, NIH-funded researchers engineered mice with deletions of genes in the synuclein family (mutations in alpha-synuclein are known to contribute to some inherited forms of PD). The investigators have used these mice to evaluate the impact of each specific gene on neuronal function. This study has expanded the body of knowledge about the function of these complex proteins, and the basic biology of PD.

A specific genetic mutation, the A53T missense mutation, has been implicated in human PD. In order to explore the different physiological pathways coded by this gene and its influence in PD development and progression, a P1 artificial chromosome (PAC) was created in which the A53T mutation was incorporated. Using this PAC, nine mouse lines have been engineered that produce the mutant protein.

In addition to manipulating genes to generate useful animal models, researchers continue to use environmental exposures to produce critically needed models. For example, NIH-funded investigators demonstrated that exposure of rats to toxicants that inhibit normal protein degradation systems in the cell can produce a slowly progressive parkinsonian syndrome, characterized by slowness of movement, rigidity, and problems with posture; destruction of neurons in the substantia nigra and several other brain regions affected in PD; and the presence of cellular structures resembling Lewy bodies, hallmark features of PD, in affected neurons. These data not only provide evidence that effects on this system by environmental exposures can contribute to the development of PD, but they also make a novel animal model - and one that recapitulates several critical features of PD - available for further investigation.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

The FY04 target had to be adjusted because the mouse was found to metabolize rotenone 300% faster than the rat. This finding created a hurdle in making a mouse rotenone model. Studies were initiated with a pesticide toxicologist to determine the actual P-450 metabolic enzyme and an inhibitor for this effect. Both were identified and initial plans were made to simultaneously administer a metabolic inhibitor with rotenone. After more extensive discussions, however, this strategy was not pursued in light of predicted complications resulting from interactions between the inhibitor and the pesticide over the course of chronic dosing. Instead, efforts were focused on developing a dosing protocol in mice using doses of rotenone that could produce partial loss of dopamine. It was recognized that such a partial lesion model may prove ideal as a susceptibility model of PD for exploring gene-environment interactions in PD and could avoid the added complication of using a metabolic inhibitor. The target was then changed to accommodate this scientific insight.

SRO-5.1 BY 2007, EVALUATE THE EFFICACY OF THREE NEW TREATMENT STRATEGIES FOR HIV INFECTION IN CLINICAL TRIALS IN AN EFFORT TO IDENTIFY AGENTS OR COMBINATIONS OF AGENTS THAT ARE MORE EFFECTIVE, LESS TOXIC, AND/OR SIMPLER TO USE THAN THE CURRENT RECOMMENDED HIV TREATMENT REGIMENS.

BACKGROUND

Prevalence/Incidence

AIDS has killed more than 22 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide. At the end of 2003, an estimated 40 million people worldwide were living with HIV/AIDS, 37 million adults and 2.5 million children younger than 15 years of age. In addition, over 3 million people died from AIDS in 2003, and 5 million people were newly infected with HIV of which 700,000 were children. A recent UNAIDS report stated, "Beyond Sub-Saharan Africa more recent epidemics continue to grow in China, Indonesia, Papua New Guinea, Viet Nam, several Central Asian Republics, the Baltic States, and North Africa". In the United States, an estimated 886,575 people are living with HIV/AIDS. Although new infections in the U.S. have remained relatively stable at approximately 40,000 new infections per year, HIV infection rates are continuing to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people older than 50 years of age.

Disease Burden

The impact of AIDS on developing nations and many countries of the former Soviet Union is profound. Lost productivity and profitability, the cost of sickness and death benefits, and the decline in a skilled workforce in the developing world will have economic effects worldwide. AIDS is affecting the military capabilities of some countries, as well as international peacekeeping forces. In Africa, the epicenter of the pandemic, AIDS is sabotaging economic development, leading to famine and massive social breakdown and creating a generation of orphans.

Rationale

NIH supports a comprehensive therapeutics research program with the goal of developing new and better approaches to prevent, treat, and control HIV infection and its associated illnesses. Basic research on HIV continues to provide a strong foundation for the identification of new viral and cellular targets, as well as the design and development of better antiretroviral drugs and treatment regimens. Groundbreaking NIH-

sponsored structural biology research has provided important insight into key viral proteins and enzymes and has been translated into the design of lead compounds with specific anti-HIV activity.

NIH-supported clinical trial networks, with over 100 U.S. and international sites at major medical centers, academic institutions, and community-based clinics, conduct Phase I, II, and III clinical studies designed to evaluate the safety and efficacy of drug regimens to treat and control HIV disease among adults, adolescents, and children as well as to prevent mother-to-child transmission (MTCT) of HIV. The standards of care for the treatment of HIV infection and its associated illnesses in the United States and Western Europe are based on important clinical findings from NIH-sponsored clinical trials.

Building on the successful demonstration in 1996 that highly active antiretroviral therapy (HAART), including a protease inhibitor (PI) and two other antiretroviral (ARV) drugs, results in significantly decreased viral loads and increased CD4 levels, NIH-supported studies have continued to define treatment regimens that slow disease progression. These powerful drug combinations have resulted in a decline in the incidence of new AIDS cases and HIV-related death rates. Since 1996, several new classes of ARVs, including fusion inhibitors, PIs, and nucleotide analogs, have been developed and shown to be safe and efficacious. Although these multiple drug combinations can successfully reduce viral load and restore immune responses, in many HIV-infected individuals, metabolic and morphologic complications associated with these treatment regimens present significant morbidity and mortality, thus warranting additional investigation.

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

HIV therapeutics research entails the development of drugs and drug regimens to target HIV infection; prevent MTCT; and prevent and treat the various opportunistic infections, co-infections, cancers, and other clinical manifestations associated with HIV disease. In the area of anti-HIV drugs, NIH will participate in the development of a minimum of three new anti-HIV compounds from existing and new classes of antiretrovirals, including agents that interfere with the viral life cycle.

NIH will initiate four new clinical trials of anti-HIV drugs and/or anti-HIV multidrug regimens to identify treatment regimens with fewer toxicities and side effects, improved bioavailability, minimal development of drug resistance, and easier compliance. NIH also plans to recompete the grants supporting the therapeutic clinical trials networks to achieve a more effective and efficient system for the conduct of Phase I, II, and III clinical trials in domestic and international settings. NIH will also develop and/or test one new approach that may inhibit MTCT. NIH is initiating studies to examine the impact of preventive MTCT regimens on future treatment options. NIH also will develop and/or test two agents for the prevention or treatment of HIV-associated manifestations, such as co-infections with hepatitis C virus or hepatitis B virus, opportunistic infections (including tuberculosis), cancers, neurological disorders, or organ-specific complications.

PART TARGETS FY 2005

The FY 2005 PART targets for achieving this goal are as follows: 1) Develop 3 anti-HIV compounds; 2) Initiate 4 drug clinical trials; 3) Develop/test 2 agents to prevent/treat drug complications; and 4) Develop/test 1 new approach to inhibit mother-to-child transmission.

PERFORMANCE MEASURES	BASELINE					
Increase the ability of resource-poor countries to conduct clinical trials for the treatment and prevention of HIV disease by providing training and capacity building at 4 sites.	(FY02) 12 AACTG sites and 10 PACTG sites	•				
Actual Performance: (MET) Sites in resource-poor countries are better able to conduct HIV clinical trials as a result of training.						
Participate in the development of two agents for the prevention or treatment of HIV-associated manifestations, such as co-infections, opportunistic infections, cancers, neurological disorders, or organ-specific complications.	(FY03) 23 approved antiretroviral drugs exist for HIV infection treatment					
Actual Performance: (MET) NIH has supported studies to develop treatments for three HIV-associated manifestations, hepatitis C virus (HCV), Cryptococcal meningitis (CM) and central nervous system (CNS)-associated neurological disease in individuals with HIV.						
Initiate clinical trials of new anti-HIV drugs and/or anti-HIV multidrug regimens in U.S. and international clinical trial sites.	(FY03) Clinical trials for the next generation of fusion inhibitors and lead compounds representing integrase inhibitors are being completed			o		
Actual Performance: Performance results will be reported in February 2006.						
Evaluate interventions to reduce mother to child transmission (MTCT) of HIV and assess the impact of these interventions on future treatment options for women and children.	(FY04) Antiretroviral therapy has dramatically reduced MTCT in the developed world; many developing countries are implementing preventive MTCT programs using nevirapine and other antiretroviral regimens				o	
Actual Performance: Performance results will be reported in February 2007.						

• **Target Active** • **Target Met** -> **Target Extended** **X** **Target Not Met**

Summary of FY04 Performance Results

Target. The FY 2004 performance target was met and exceeded because NIH has supported studies to develop treatments for three (one more than planned) HIV-associated manifestations, hepatitis C virus (HCV), Cryptococcal meningitis (CM), and central nervous system (CNS)-associated neurological disease in individuals with HIV infection. During FY 2004 two important studies were published that advanced treatment for individuals dually infected with hepatitis C virus (HCV) and HIV and for HIV-infected individuals with cryptococcal meningitis (CM). CM is caused by the fungus *Cryptococcus neoformans* and remains the most common life-threatening infection of the central nervous system in HIV-infected individuals.

In a study conducted by the NIH-funded Adult AIDS Clinical Trials Group (AACTG), the treatment combination of peginterferon and ribavirin was found to be a superior treatment for HIV-infected individuals with HCV, a major cause of morbidity in HIV-infected individuals. Mortality from CM is high in the absence of appropriate therapy. Utilizing an animal model of CM infection, NIH-supported scientists determined that the combination of amphotericin B plus fluconazole exhibited better antifungal potency compared to amphotericin B alone, amphotericin B plus flucytosine, or fluconazole plus flucytosine. These findings have contributed to the design of an international human Phase II clinical trial to address the need for more effective antifungal therapy for CM.

NIH has funded studies to assess the impact of improved penetration of antiretrovirals into the central nervous system (CNS) in individuals with HIV- associated neurological disease. One study evaluated

whether cerebrospinal fluid (CSF) drug penetration and CSF virologic suppression influence the extent of neuropsychological improvement during ART. Regimens containing CSF penetrating drugs showed significantly greater reduction of CSF viral load, as well as improved neuropsychological performance. These findings suggest that including CSF-penetrating drugs in the ART regimen and monitoring CSF viral load may be indicated for individuals with HIV-associated cognitive impairment.

IMPLEMENTATION STRATEGY ADVANCES OR OTHER HIGHLIGHTS. DURING THE PAST YEAR, MORE THAN 3000 COMPOUNDS WERE SCREENED FOR ACTIVITY AGAINST HIV-1 REV OR TAT. POTENTIAL LEAD COMPOUNDS ARE UNDERGOING ADDITIONAL TESTING. A NEW THERAPY, PA-457, WHICH SHOWED PROMISE IN A MURINE MODEL, IS CURRENTLY BEING TESTED IN A PHASE II CLINICAL TRIAL.

In FY 2004, NIH organized a workshop entitled, "Mother to Child Transmission of HIV." As a direct result of that meeting, NIH developed clinical trials to investigate strategies to minimize the development of nevirapine (NVP) resistance in mothers exposed to single-dose NVP and clinical trials to explore the effects of previous exposure to single-dose NVP on future antiretroviral therapy for women and infants. NIH-supported researchers have shown that a combined treatment of short courses of both AZT and NVP resulted in an 80 percent lower MTCT rate compared to using AZT alone which is similar to those achieved with the three-drug regimens routinely prescribed in developed countries. These results led to changes in WHO treatment recommendations and to the standard of care in Thailand. The NIH International Site Development Initiative (NISDI) is providing training and infrastructure development in Latin America and the Caribbean.

A study of three regimens for the initial treatment of HIV showed triple-nucleoside regimens are virologically inferior to regimens containing efavirenz for treatment- naive patients. Another study will be conducted in India, Thailand, Brazil, Malawi, Zimbabwe, and the United States to examine the comparative efficacy of different ARV regimens. Other studies underway will: compare the safety and efficacy of adefovir and tenofovir for patients co-infected with hepatitis B virus and HIV; and examine whether the long-term effects of pegylated-interferon alfa-2a use reduces the rate of liver damage in patients with HCV and HIV co-infection who have failed to clear HCV infection with previous treatment.

NIH also supports the development of agents to treat neurological disorders associated with HIV infection. NIH funded a clinical trial to assess the potential utilization of valproic acid as a neuroprotective strategy for HIV-associated neurologic disease. NIH-supported researchers recently validated a monkey model of HIV-associated neurological conditions and discovered that brain-derived neurotrophic factor can protect cultured nerve cells from HIV-induced damage.

NIH-sponsored research evaluates the mechanisms of action of ARVs, interactions of other drugs, and the effects of nutrients on HIV disease progression. Studies are being conducted to pinpoint the basis for the development of mutations in HIV protease and reverse transcriptase that result in drug resistance. These studies are leading to new antivirals with improved resistance profiles. Zinc deficiency and the role of other micronutrients have been shown to be factors in HIV disease progression. As a result of these findings, a study was funded in FY 2004 to test whether a reformulated multi-vitamin supplement would slow progression of HIV/AIDS.

NIH also supports studies that focus on cancer and cardiovascular manifestations associated with HIV infection and antiretroviral treatment. NIH continues to support the AIDS Malignancy Clinical Trials Consortium which is developing and evaluating novel, mechanism based treatment and prevention regimens for HIV-related cancers. Additionally, NIH supports research to evaluate HIV lipodystrophy and cardiovascular complications associated with ART and protease inhibitor therapy.

EFFICIENCY. THE FY04 TARGET HAS BEEN MET AND EXCEEDED. NIH SUPPORTED STUDIES TO DEVELOP TREATMENTS FOR THREE HIV-ASSOCIATED MANIFESTATIONS, ONE MORE THAN HAD BEEN PLANNED.

PART Progress on Key Performance Measures FY 2005

NIH continues to make progress toward achieving the FY 2005 PART targets for the HIV/AIDS Research Program goal: to evaluate the efficacy of three new treatment strategies for HIV infection.

Progress towards each of the AIDS therapeutics research targets includes: 1) three lead anti-HIV compounds are progressing through the drug discovery and drug development pipeline; 2) four clinical protocols are being developed and enrollment will be initiated for the conduct of phase I, II, and/or III clinical trials of drug combinations against HIV and its associated coinfections, opportunistic infections, and malignancies; 3) two potential agents and lead compounds against drug-associated complications are undergoing drug development, pre-clinical testing, and/or evaluation in clinical trials; and 4) studies are underway in domestic and international sites to develop and evaluate a safe, effective, affordable, and sustainable intervention to block mother-to-child transmission of HIV, including transmission associated with breastfeeding.

SRO-5.2 BY 2009, DETERMINE THE EFFICACY OF STATINS IN PREVENTING PROGRESSION OF ATHEROSCLEROSIS IN CHILDREN WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE, OR LUPUS).

BACKGROUND

Disease Burden

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

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

Rationale

Atherosclerosis is a thickening of the inside walls of arteries that is caused by the gradual buildup of fatty substances in arteries. This thickening narrows the space through which blood can flow and can result in heart attacks or strokes. Atherosclerosis usually occurs when a person has high levels of cholesterol (a fat-like substance), which can build up on the walls of arteries. Women and children with lupus have a significantly increased risk for cardiovascular complications related to premature atherosclerosis. The

data on cardiovascular and lipid abnormalities in children with lupus implicate atherosclerosis as an important potential source of long-term morbidity and mortality. Statins are drugs that lower cholesterol in blood and decrease the risk for atherosclerosis and cardiovascular disease (CVD). Statins not only decrease mortality and morbidity from coronary artery disease in adults but also have intrinsic anti-inflammatory properties, which may be especially beneficial in lupus.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A five-year study, known as the APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythymatosus) trial, will test 280 children diagnosed with systemic lupus erythematosus (SLE). The double-blind, placebo-controlled trial will randomize patients to receive either statins or a placebo for 36 months. Atherosclerosis will be 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 also they have intrinsic anti-inflammatory properties, which may be especially beneficial in lupus. This is a multi-center, prospective, randomized, double-blind intervention study for children with lupus and involves 20 centers from the Childhood Arthritis and Rheumatology Research Alliance (formerly the Pediatric Rheumatology Research Network) and will enroll a total of 280 children with recent-onset lupus who will be treated with the medication atorvastatin for 36 months, establishing the largest cohort of pediatric lupus patients ever prospectively studied in the United States.

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 includes (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 will be used for trial randomization and drug kit assignment, which takes advantage of novel and efficient technologies that improve trial conduct and cost-effectiveness.

Conducting additional related studies increases the value of a clinical trial, and the design of this trial includes the development of ancillary, mechanistic substudies to explore the processes that contribute to disease progression. These additional studies will leverage the value of the investment made by NIH in terms of scientific knowledge as well as improve the integration of translational research from this clinical trial.

The study staff plans to develop approaches to improving carotid intima medial thickening (IMT) certification rate, IRB approval rate, contract execution and regulatory documents. To maintain enthusiasm in enrolling sites and in sites not yet activated, the study staff will hold regular conference calls and training sessions as well as promote sharing of positive experiences between sites. To assure that enrollment of 75% is complete by 2006, the investigators plan to activate sites as quickly as possible and replace non-performing sites quickly.

Baseline data analysis on enrolled patients will be complete in FY 2006, including any adverse events. Data on monitoring study progress and adverse events will be routinely provided from the clinical sites to the NIH.

PERFORMANCE MEASURES	BASELINE					
Complete the training of personnel involved in conducting the trial, including sonographers 1U&C UpCltlLlllg L11C llILCltlCLIVC V U1CC Res' onse System.	(FY02) Standard operating procedures are being completed but training not yet done		•			
Actual Performance: (MET) Training of all appointed sonographers has been completed.						
Launch patient enrollment in at least 10 of the 20 ,1 ,,,,d ,it ,,	(FY03) Protocol for patient enrollment established		•			
Actual Performance: (MET) There are currently 16 sites actively recruiting patients into the study.						
Conduct ancillary studies, leveraging the investment of the trial in areas related to the determination of the efficacy of statins in preventing progression of atherosclerosis in children with lupus.	(FY03) One ancillary study approved to assess the effect of statins on blood cells			o		
Actual Performance: Performance results will be reported in February 2006.						
Complete baseline data analysis on the remaining enrolled patients, including any adverse events.	(FY04) 14% of patients are enrolled and data analysis of these enrolled patients is complete, including any adverse events				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met — Target Extended X Target Not Met

Summary of FY03 Performance results

Target 1. The target has been met. Training of all appointed sonographers has been completed. Sonographer certification and re-certification is ongoing as per trial standard operating procedures.

Summary of FY04 Performance Results

Target 2 This target has been met. There are currently 16 sites actively recruiting patients into the study.

Implementation Strategy Advances or Other Highlights. One ancillary study was implemented to evaluate the production of nitric oxide (NO) metabolites in APPLE trial participants. The research protocol for this ancillary study was reviewed and approved by the Data and Safety Monitoring Board (DSMB). The principal investigator of the ancillary study produced additional preliminary data in support of the techniques and procedures to be used. Also, the APPLE trial staff developed procedures to (1) solicit and handle other ancillary study projects and (2) have the DSMB review and approve such ancillary studies.

SRO-5.3 BY 2009, EXPAND THE RANGE OF AVAILABLE METHODS USED TO CREATE, ANALYZE, AND UTILIZE CHEMICAL LIBRARIES, WHICH CAN BE USED TO DISCOVER NEW MEDICATIONS. SPECIFICALLY, USE THESE CHEMICAL LIBRARIES TO DISCOVER 10 NEW AND UNIQUE CHEMICAL STRUCTURES THAT COULD SERVE AS THE STARTING POINT FOR NEW DRUGS.

Background

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

Rationale

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

NIH funding is leading to the discovery of new chemical library methods, which in turn will enhance the range and quality of chemical compounds available for drug discovery. Rapid and efficient biological screening of improved chemical libraries may speed the discovery of new medicines.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A total of four Centers of Excellence in Chemical Methodologies and Library Development have been established and five new centers and seven planning grants were funded to develop natural products drug discovery programs under the International Cooperative Biodiversity Groups Program. In FY 2004 and beyond, these centers, and new initiatives to be supported through the NIH Molecular Libraries and Molecular Imaging Roadmap, will focus on (1) developing innovative methods of synthesis and library creation; (2) increasing the sharing of knowledge among researchers, (3) increasing access to research results by exploring and developing systematic means to inventory newly created chemical libraries and methods of synthesis, (4) biologically screening the libraries and inventorying the outcomes of these screening procedures as new libraries are created, and (5) coordinating and setting priorities for these initiatives through the use of scientific advisory groups.

PERFORMANCE MEASURES			FY 2004	
Fund two additional Centers of Excellence for Chemical Methods and Library Development to develop chemical libraries and high-throughput methods for screening potential therapeutic compounds.	(FY02) Prior to FY 2003, only two centers existed			
FY 03	*Actual Performance:* (MET) Two additional Centers of Excellence for Chemical Methods and Library Development were established at Harvard Medical School and the University of Kansas.			
Investigate at least six innovative methods to synthesize chemical libraries and employ successful methods to create new libraries	(FY03) High throughput methods for making chemical libraries for drug development are limited			

PERFORMANCE MEASURES	BASELINE					
through the funded Centers. Ensure that inventories of libraries and successful methods are established so that the results of this work can be readily accessible to the scientific community for drug development.						
Actual Performance: (MET) Established CMLD centers investigated at least ten (10) innovative methods to synthesize new chemical libraries while making results of these new libraries and successful methods available to the scientific community.						
Facilitate the identification of promising therapeutic compounds by funding the biological screening of chemical compounds contained in the libraries and provide an inventory of the results.	(FY03) CMLD centers are currently being established; screening of their libraries has not yet begun			o		
Actual Performance: Performance results will be reported in February 2006.						
Begin development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products).	(FY03) Due to the expense and the time required to isolate, purify, and identify new compounds, few pharmaceutical companies include natural products in their drug discovery programs				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met -> Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 was met because established CMLD centers investigated at least ten (10) innovative methods to synthesize new chemical libraries while making results of these new libraries and successful methods available to the scientific community. The FY 2004 target was to investigate at least six innovative methods to synthesize chemical libraries and employ successful methods to create new libraries through Centers for Chemical Methods and Library Development (CMLD). The FY 2004 target also involved making libraries and methods readily accessible to the scientific community. Both aspects have been successfully implemented.

Each CMLD center features a team of faculty-level project leaders working synergistically on several method-related projects. Each center also includes a library synthesis core facility (i.e., personnel plus equipment), the purpose of which is to validate new methodologies and to carry out the synthesis of chemical libraries using these new methodologies as well as other, existing methodologies, as necessary. These new methodologies are made available to the scientific community through publications, and information on compound libraries generated by the CMLD centers will be accessible through NIH's PubChem web-based application. In FY 2004, the following CMLD projects were supported, and the methods investigated in each of these projects were used to synthesize new chemical libraries:

- Development of a Stereochemistry-Dependent Folding Process and Application to Diversity-Oriented Synthesis
- Branching Pathways Based on Reactive Intermediates
- Convergent, Diversity-Oriented Synthesis of Hybrid Alkaloid Libraries
- Synthesis of a Focused Library of Eg5 and ATR Inhibitors Using the Lantern Platform
- Microwave-Assisted "Libraries from Libraries" Approach toward Allylic Amides and C-Cyclopropylalkylamides
- Three-Step Conversion of Amino Acid Containing a-Alkylidene Cyclopentenones to Tricyclic Acylpyrroles

- **P**-Amino Acid-derived Peptide Libraries: Polypeptide Diversity using Unnatural **P**-Azido Acid Building Blocks
- Stereoselective Synthesis of Polypropionate-Derived Libraries: Synthesis of Heterodimeric and Homodimeric Macrodiolides
- Synthesis and Elaboration of Novel Scaffolds Containing Positional and Stereochemical Diversity: Synthesis of Highly Functionalized Epoxyquinol Scaffolds and Related Libraries
- Convergent, Diversity-Oriented Synthesis of Complex Molecules Through Domain Shuffling

Implementation Strategy Advances or Other Highlights. In addition to these outcomes specific to the FY 2004 target, there were other advances related to this goal. The International Cooperative Biodiversity Groups (ICBG), managed by NIH and funded cooperatively with the NSF and the USDA, have developed access and benefit sharing agreements and contracts to establish multidisciplinary, multi-institutional international consortia for natural products drug discovery. Several of the Groups have experimented with methodologies to enhance meaningful hit rates in bioassays and have optimized assays to utilize more appropriate technology in developing countries. A meeting sponsored by NIH's Malaria Research and Reference Reagent Resource Center was held for representatives from all groups to discuss strategies to identify potential malaria drugs, which was followed by a meeting to share methodologies and progress. Training in the use of the Natural Product Information System database was carried out for data managers from each program as well as training on the database at several of the foreign sites.

In June 2004, NIH announced the establishment of the NIH Chemical Genomics Center, the first component of a nationwide network that will produce innovative chemical "tools" for use in biological research and drug development. The Center plans to begin high-throughput screening of small molecules by the end of 2004. Up to 10 pilot centers will be funded at academic institutions and other locations across the country in FY 2005.

NIH also continues to support a Resource Center for Solid State NMR of Proteins at the University of California, San Diego (UCSD), where researchers have developed a technology that will enable high-throughput structure determination. This technology can be applied to the high-throughput screening of chemical libraries. Researchers are also using this technology to determine the structure of G-protein coupled receptors, the major class of drug receptors, which may aid in the development of new therapeutic agents.

Three program project grants have been funded to foster new technologies for the generation of compound libraries and novel assays for anticancer drug discovery. NIH recently issued a program announcement (PA) for the "Development of Assays for High Throughput Drug Screening." The purpose of this PA is to solicit research on the discovery and development of new and innovative assays that may be adaptable for automated screening, helping scientists identify new tools for basic research and new leads for therapeutics development.

Efficiency. CMLD centers were designed and implemented to create collaborations between scientists in ways that did not exist previously by fostering interactions, communications, and conferences between investigators committed to the development of new methodologies. Therefore, as advancements in technologies or methodologies occurred, analyses and applications were developed in less time than had been planned. While investigations of six innovative methods to synthesize chemical libraries were planned, an additional four methods (for a total of ten) were actually studied.

PART

This goal was included in the FY2006 PART of the Extramural Research Program. See Section C.1 to review results and recommendations.

SRO-5.4 **BY 2007, IDENTIFY 20 SMALL MOLECULES THAT ARE ACTIVE IN MODELS OF NERVOUS SYSTEM FUNCTION OR DISEASE AND SHOW PROMISE AS DRUGS, DIAGNOSTIC AGENTS, OR RESEARCH TOOLS.**

BACKGROUND

Disease Burden

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

Rationale

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

Recent advances in understanding the nervous system and the completion of the Human Genome Project have provided an enormous cache of new biology to be studied and potential new drug targets to be investigated. Carefully designed small molecules can be powerful modulators of gene function; this principle underlies their use as basic research tools and as pharmaceuticals. The objectives of this goal are to (1) identify research tools and candidate therapeutics among currently available small molecules and (2) make new small molecules available to the public sector to further stimulate basic research and drug discovery.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH will create a publicly available physical repository of 750 selected bioactive compounds to facilitate access and evaluation for therapeutic potential, diagnostic use, or use as research tools in neurobiological and other research. This number of compounds should be sufficient to yield multiple hits in most assays (tests), yet is small enough to be utilized without robotic equipment, making the collection broadly and immediately useful to investigators in both academia and industry. This project involves identifying candidate compounds; evaluating the quality of the existing data for candidate compounds; creating a database of the chemical, pharmacological, and toxicological properties of selected existing compounds; and creating physical repositories of selected compounds and drugs for use in neurobiological and other research.

Utilizing High-Throughput Screening (HTS) approaches, NIH will identify potential research tools and drug leads for neurological disorders. Activities will include screening at least three neurodegenerative disease assays per year with a set of 100,000 compounds at the HTS Facility for Neurodegenerative Disease; developing a cost-effective, high-throughput behavioral screen to identify molecules with promise for treating alcohol abuse and dependence; and completing the screening of four novel chemical libraries—with a total of more than 80,000 compounds—for activity at D1 dopamine receptors to develop a selective D1-dopamine receptor agonist as a potential treatment for cocaine addiction.

Through the Anticonvulsant Screening Project (ASP), a public-private partnership, small molecules will be identified that can be used for potential anticonvulsant treatments, including drug-resistant epilepsy and epileptogenesis. This program will need to enroll new industrial and/or academic suppliers of small molecules with potential anticonvulsant activity and test additional compounds to identify potential drug development leads.

A contract-based approach is being explored as a new paradigm for accelerated funding and milestone-driven management for therapy development in rare diseases. A project focused on spinal muscular atrophy (SMA) was initiated in FY 2003, and calls for research proposals will be issued in accordance with a 4-year research plan that addresses all preclinical aspects of therapeutics development. FY 2004 Request for Proposals will be issued to establish centralized facilities that focus on compound development, testing compounds in cell-based models, and testing promising compounds that emerged from cell-based assays in mouse models of SMA. Compounds that prove to be safe and effective in animal models of SMA eventually may be tested in SMA patients in controlled clinical trials.

The National Cooperative Drug Discovery Group Program (NCDDG) model will be expanded to advance the development and testing of fundamentally new, rationally designed medications and treatments for mental disorders and nicotine addiction (MD/NA). The NCDDG-MD/NA will (1) accelerate the discovery of new therapeutics for mood disorders and nicotine addiction, (2) increase the availability of pharmacologic research tools for basic and clinical research, and (3) facilitate the development and validation of models to evaluate novel therapeutics in mood disorders.

Tremendous opportunities exist for the application of positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging in studies of the pathophysiology and treatment of brain disorders, but relatively few radioligands are currently available for functional imaging of target molecules implicated in normal brain function and aging and in brain and behavioral disorders. Several NIH ICs will stimulate collaborations with industry and academia to create novel radioligands for PET and SPECT imaging in the human brain. This initiative is intended to facilitate the development of (1) PET and SPECT probes for molecular targets that are of broad interest to the neuroscience research community, and (2) new technologies for radiotracer development.

PERFORMANCE MEASURES	BASELINE				
Expand the National Cooperative Drug Discovery Group Program model to target mental disorders and nicotine addiction to advance the development/testing of fundamentally new medications/treatments for mental disorders and nicotine addiction.	(FY02) None of the NCDDG Programs focus on mood disorders and nicotine addiction	•			
Actual Performance: (MET) Three grants modeled on the National Cooperative Drug Discovery Group (NCDDG) Program were awarded for development/testing of new medications/treatments for mental disorders and nicotine addiction. Prior to these awards, the NCDDG did not address these conditions.					
Identify potential research tools and drug leads for neurological disorders by developing/utilizing high-throughput screening programs, including assay development.	(FY03) 1,040 FDA-approved drugs and >23,000 potential anti-epileptic compounds screened		•		
Actual Performance: (MET) 76 promising compounds identified in various assays; 2 potential epileptic therapies advanced to clinical testing. Proof-of-concept tests initiated for alcohol abuse and addiction screening.					
Create a publicly available collection of 750 bioactive compounds, with defined activity in [illegible], and government sources, to be used in screens for potential drugs, research tools, and diagnostic agents.	**(FY03) Known bioactive compounds require further evaluation of activity and improved availability**			**o**	
FY *Actual Performance:* Performance results will be reported in February 2006.					

Test the ability of at least one promising compound to extend survival and reverse molecular effects of SMA in a mouse model of the disorder.	(FY04) SMA program established; 3 promising compounds identified in screens; SMA mouse models available	: : : O	
	Actual Performance: Performance results will be reported in February 2007.		

O Target Active • Target Met Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The target was met: the Neurodegeneration Drug Screening Consortium identified compounds that reduce the effects of familial dysautonomia-associated mutations in cell culture models (the plant cytokinin kinetin), prevent the molecular cascade leading to spinobulbar muscular atrophy (four compounds); protect cells from death in a Huntington's disease assay (18 compounds), prevent protein aggregation associated with a number of neurodegenerative diseases 25 compounds), and may serve as the basis for drugs to treat stroke and neurodegeneration or as new research tools for understanding mitochondrial roles in neuronal cell death (28 compounds). One of the compounds identified in a screen for ALS drugs, ceftriaxone, advanced to the point of entering clinical trials in FY04. Also, more than 70 potential drugs for treating epilepsy have been screened *in vivo* through the ASP. Three compounds have advanced to the stage of preclinical testing, and two others (including compound ICA-69673) have advanced to the point of entering clinical trials.

The NIH has initiated preliminary proof-of-concept tests to examine whether four rodent strains are appropriate for use in a behavioral screen for molecules to treat alcohol abuse and dependence.

Implementation Strategy Advances or Other Highlights. NIH released six Requests for Proposals under the SMA program that will fill a need for a mouse testing facility, an *in vitro* testing facility, and a medicinal chemistry facility for potential SMA drugs, as well as the development of models and reagents to be used at the contracted facilities.

NIH support led to the publication of peer-reviewed journal articles on the development of novel compounds to treat pain, alcohol addiction, and cocaine addiction.

Working under an NIH contract, chemists assembled a list of approximately 2000 compounds that met defined criteria for bioactivity, stability, purity, and other factors important for inclusion in the bioactive compound collection.

NIH-supported researchers have recently developed the first radiotracer for PET imaging of amyloid plaques, a characteristic pathological feature of Alzheimer's disease, in living subjects. NIH support also led to several recent papers on and patent applications for a number of new PET radiotracers that recognize specific neurotransmitter receptors.

SRO-5.5 BY 2008, DEVELOP AND TEST TWO NEW RESEARCH-BASED TREATMENT APPROACHES FOR DRUG ABUSE IN COMMUNITY SETTINGS.

BACKGROUND

Prevalence

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

Disease Burden

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

Rationale

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

One important tool to treat substance abuse is behavioral treatment, which has been documented to be effective in improving drug abuse and drug addiction outcomes. Recent promising findings have been achieved by interventions that target specialized populations: e.g. minorities, adolescents, families, and women diagnosed with Post-Traumatic Stress Disorder (PTSD). Brief Strategic Family Therapy (BSFT) is a family-based intervention aimed at preventing and treating child and adolescent behavior problems, including substance abuse, in inner city, minority families. A second research-based treatment for community settings is Seeking Safety, a cognitive-behavior substance abuse intervention for women with a DSM-IV diagnosis of PTSD. Estimates suggest that 80% of women seeking treatment for drug abuse have histories of assault. Women who suffer from both PTSD and Drug Abuse have a more difficult time meeting their treatment goals. Finding effective treatments for this high-risk population is important. Early studies show Seeking Safety is a treatment option with a great potential for this population. This study will examine the effectiveness of this treatment combined with standard substance abuse treatment. Another research-based treatment to be used in community settings is Motivational Enhancement Treatment (MET), a systematic intervention based on principles of motivational psychology. More than two decades of research have shown strong support for using MET for alcohol, cigarettes, and abused drugs. It has been demonstrated effective for improving treatment engagement, retention, and outcome for substance users. The therapeutic usefulness of incorporating MET into the standard drug abuse treatment entry of community treatment programs will be tested in this study.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

underserved in drug and alcohol abuse treatment centers. Several other research-based treatments for alcoholism are being adapted and tested in community settings. Potentially these will contribute to treatments available to the community.

In FY 2005, drug and alcohol treatment providers will be trained to deliver standardized behavioral treatment interventions of BSFT, Seeking Safety, and MET to patients within the framework of the clinical trials research design. Treatment providers will be trained to maintain data on patient's symptoms, behavior, and drug use to determine clinical and research outcomes. To ensure treatment protocol adherence treatment providers will be videotaped, supervised, and monitored. Also during FY 2005, outcome data for patients will be collected at regular intervals on substance abuse, risk behaviors, and comorbid psychiatric symptoms to determine the overall treatment effects of the evidence-based interventions.

During FY 2006, recruitment of approximately 1000 patients will be completed for participation in BSFT, Seeking Safety, or MET treatment protocols.

In order for NIH to be successful in achieving this goal, a series of ambitious steps have been planned. These steps include building the treatment research infrastructure necessary followed by recruitment of 1000 patients from specialized populations to participate in these research and community-based treatment approaches.

PERFORMANCE MEASURES	BASELINE					
Adapt two treatment approaches from small-scale research settings to community-based settings for the purpose of bringing research-based treatments to communities.	(FY03) No randomized clinical trials have delivered BSFT and Seeking Safety to these specialized populations					
Actual Performance: (MET) Three treatments have been adapted for community-based settings.						
Build capacity for targeted treatments by training 90 treatment providers to: (a) participate in clinical trials to promote treatment fidelity; and (b) deliver evidenced-based behavioral treatment to target populations in community settings.	(FY03) Fewer than 25 treatment providers have been trained to deliver BSFT and Seeking Safety to these specialized populations in randomized clinical trials in community settings			o		
Actual Performance: Performance results will be reported in February 2006.						
Recruitment will be completed of approximately 1000 patients from specialized populations to test the efficacy of community-based treatments.	(FY 04) Enrollment of subjects for Seeking Safety, BSFT, and MET was initiated.				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met Target Extended ° Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target to adapt treatment approaches to community-based settings has been met. Three treatments, MET, Seeking Safety, and BSFT, have been adapted for communities and these communities include special populations. Highlights of adaptation include site selection and preparation of materials, such as informational pamphlets and others, that are appropriate for each site. For example, the BSFT approach targets a Hispanic population. Therefore, for the BSFT approach, Spanish language translation units were established to adapt the materials, and Spanish language training for staff was provided. Another aspect of adapting MET, Seeking Safety, and BSFT into

community-based settings involved setting up infrastructure within each setting to support clinician training and supervision.

Implementation Strategy Advances or Other Highlights. Several advances in implementation have been made. Recruitment activities have been initiated for the treatment protocols. Twenty-one sites are participating in the studies to date, six of them in MET treatment, seven in Seeking Safety, and eight in BSFT. The training of treatment providers in the community is on-going, and adaptation into the community treatment settings has been successful. Training materials have been developed and are accessible on the web, recruitment brochures have been developed, and information about the protocols has been posted on the web.

Efficiency. NIH has met and exceeded the FY04 target by adapting three evidence-based treatments to community-based settings. While initial plans estimated that adapting two treatments would be feasible, three treatments were in fact included in the study.

SRO-6.1 BY 2012, IDENTIFY THE GENES THAT CONTROL THE RISK OF DEVELOPMENT OF AGE-RELATED MACULAR DEGENERATION (AMD) AND GLAUCOMA IN HUMANS.

BACKGROUND

Prevalence/Incidence

Age-related macular degeneration (AMD) is a sight-threatening degenerative eye disease that affects the part of the retina known as the macula and leads to varying degrees of vision loss depending on the form and severity of the disease. Of the nearly 60 million people in the United States age 55 or older in the year 2000, 7.3 million are at risk of developing advanced, sight-threatening AMD in one or both eyes and 1.75 million citizens currently have AMD. This number is expected to increase to nearly 3 million by the year 2020. Glaucoma is a group of eye disorders that shares a distinct type of optic nerve damage that can lead to blindness. Approximately 2.2 million Americans have glaucoma currently, and this number will increase to over 3.3 million by the year 2020 due to the aging of the U.S. population. As many as 120,000 people are blinded from this disease.

Disease Burden

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

Rationale

The development of effective treatments for AMD has been limited by the complicated nature of the disease and the fact that the pathophysiology of the disease is poorly understood. The genes for other forms of macular degeneration, including Stargardt disease and Best macular dystrophy, have been identified and are being studied to learn whether similar disease mechanisms are involved in AMD. These genes have also been considered as candidate genes for AMD, but the results suggest a complex underlying genetic predisposition or susceptibility to biological and environmental factors in the pathogenesis of this complex disorder. Additional investigation of the genes that control this

predisposition or susceptibility may improve understanding of the disease process and ultimately lead to improved treatments or the means to prevent this disease. Glaucoma is not a single disease but rather a group of diseases characterized by a particular type of retinal ganglion cell death that is usually, but not always, associated with an increase in intraocular pressure. Current treatments, whether surgical or pharmacologic, are aimed at reducing intraocular pressure and are often inadequate in preventing vision loss. A variety of mutations have been identified that may play a role in the development of primary open-angle glaucoma. The multiple genetic loci and gene associations linked to various forms of glaucoma are other indications of the complex nature of this disease and underscore the need for additional research to clarify the roles of environmental and genetic risk factors in the pathology of this heterogeneous disease.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

Also important in progress toward this goal is making genetic material and information from well-characterized patients available to investigators. Population-based resources of blood, transformed lymphocytes, and DNA from patients with well-characterized AMD and glaucoma will be made available to investigators nationally. Because of the rigor and uniformity in characterizing the disease status of the participants, ongoing clinical trials will be used to collect specimens and create large databases of genetic information for additional analysis.

Complex diseases like AMD and glaucoma may require animal models exhibiting multiple genetic changes to produce the full range of pathologic conditions seen in these human diseases. These models can allow the further characterization of the genetic and biochemical abnormalities that lead to the disease process. After identification of potential genes related to these diseases, modifications of these genes can be introduced into animal models to determine whether they cause pathology in the animal similar to that found in humans. Several candidate genes for use in an animal model, including *fibrillin-6* and the Stargardt gene for AMD, and optineurin for glaucoma, have already been identified.

Expand the genomic resources available to vision researchers through NEI Bank and related trans-NIH activities.	(FY02) 31,000 human gene sequences; 12,000 unique human eye-expressed genes	•				
Actual Performance: (MET) Genomic resources expanded to include 30% more human gene sequences, 8% more unique human eye-expressed genes, and new DNA sequence data and clones.						
Reach consensus on a descriptive manual with standards that can be used to describe the diverse retinal phenotypes found in macular degeneration.	(FY03) No consensus descriptions on AMD phenotypes exist		•			
Actual Performance (MET) A consensus was reached on a manual of classification standards for use by fundus photograph and reading centers that will aide in maintaining useful classification systems to identify new phenotypes and allow for possible meta-analysis of retinal phenotype collections.						
Collect and make available to investigators genetic material and information from over 4,000 well-characterized patients with either AMD or glaucoma.	(FY04) DNA specimens from large numbers of well-characterized AMD or glaucoma patients are not available			o		
Actual Performance: Performance results will be reported in February 2006.						
Develop animal models of AMD and glaucoma that closely mimic the pathologic processes underlying these diseases in humans.	(FY05) Existing animal model systems for AMD and glaucoma do not closely resemble the human disease				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The target was met because a consensus was reached on classification standards that can be used to describe the diverse retinal phenotypes found in macular degeneration. To achieve the target, NIH hosted the *Age-related Macular Degeneration Phenotype Consensus Meeting.* This meeting assembled investigators with the largest AMD reading/grading collections in the U.S. and abroad. Each of the grading centers has collected phenotype data from large cohorts for various epidemiology and treatment studies. The eight centers participating in the meeting had similar classifications systems; these provide a cohesive system to read/grade AMD fundus photos and to describe new phenotypes. A consensus was reached to use these systems as a standard for the identification of future phenotypes.

Much of the current focus in retinal phenotype classification is directed toward identifying new AMD phenotypes, and devising and maintaining classification standards is essential to this effort. The identification of new AMD phenotypes will improve diagnostic accuracy, refine treatment protocols, define useful outcome measures for clinical trials, and help direct epidemiology and genetic studies to identify factors that influence various phenotypes.

Implementation Strategy Advances or Other Highlights. The standards are for use in maintaining useful classification systems to identify new phenotypes and allow for possible meta-analysis of retinal phenotype collections. By having a consensus approach, investigators around the world can utilize a "common language" to describe different stages and forms of macular disease.

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.

BACKGROUND

Prevalence

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

- In 2004, the prevalence of diabetes in the United States was approximately 18.2 million people, or 6.3 percent of the population, with approximately 90-95 percent of this number having type 2 diabetes.
- CVD accounts for two-thirds of deaths among people with diabetes.
- Chronic kidney disease is estimated to affect as many as 10 to 20 million Americans and can lead to kidney failure. While this estimate is used by advocacy groups, there is substantial uncertainty in the numbers. Unpublished internal NIH analyses suggest lower estimates for chronic kidney disease.
- The number of patients with kidney failure or end-stage renal disease (ESRD) has doubled over the past decade and now stands at nearly 400,000.
- Heart disease and stroke are the leading causes of death in patients with ESRD.

Disease Burden

The Nation faces national epidemics of both type 2 diabetes and ESRD. In 2002, the economic cost of diabetes in the United States was estimated at $132 billion. 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. Chronic kidney disease is also a significant health burden. In its most severe forms, it leads to ESRD, where either dialysis or kidney transplantation is required to maintain life. About half of new cases of ESRD have kidney disease 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. The cost of caring for the ESRD population was $19.4 billion dollars in 2000 and consumed about 6 percent of the Medicare budget.

Rationale

For both diabetes and kidney disease, premature CVD is the major cause of death. Goal 6b 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.

Goal SRO-6.2 also addresses 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, 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, its benefits in reducing CVD 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 known risk factor for CVD. Folate and B-vitamin supplementation can normalize homocysteine levels in patients with mild chronic kidney disease, their effect on CVD risk remains to be determined.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The NIH has initiated 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 realizing GPRA Goal SRO-6.2 by 2011. For example, the Goal SRO-6.2 target for FY 2006 is to provide 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.

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 total homocysteine by means of a multivitamin in clinically stable kidney transplant recipients results in a significant reduction in atherosclerotic CVD (compared with a control group whose homocysteine levels are expected to remain the same over time). The target patient recruitment **is** 4,000 kidney transplant recipients).

FREEDOM [Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease] Trial. This trial will compare, in 2,400 diabetic patients, a multivessel stenting strategy, using drug-eluting stents, to coronary artery bypass graft (CABG) surgery. The primary outcome is the difference in mortality rates between the stent group and CABG group over a 5-year period.

PERFORMANCE MEASURES	BASELINE					
Assess the effect of intensive versus conventional glycemic control on intima media thickening of the carotid artery, a marker for progression of atherosclerosis, in participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.	(FY02) No effect of intensive vs. conventional blood glucose control was seen in earlier carotid ultrasound measurements	•				
Actual Performance: (MET) Effects of intensive versus conventional glycemic control were assessed in EDIC study participants. Finding suggests that aggressive management of blood glucose levels can produce short- and long-term benefits.						
Complete recruitment for the Action for Health in Diabetes (Look AHEAD) study (5,000 patients), in order to compare the effects on cardiovascular events of an intensive lifestyle intervention designed to achieve and sustain weight loss versus support and education in obese individuals with type 2 diabetes.	(FY03) Look AHEAD had recruited about half (2,500) of its patients					
Actual Performance: (MET) Look AHEAD exceeded its target goal of 5000 obese patients who have type 2 diabetes, and enrolled 5,145 participants by May 2004.						
Complete recruitment for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (10,000 patients), which is comparing effects on CVD of intensive versus conventional interventions of lowering blood glucose, blood pressure; and treating blood lipids in diabetic patients at high risk for CVD.	(FY03) ACCORD had recruited 1,184 participants in a Vanguard phase			o		
Actual Performance: Performance results will be reported in February 2006.						
Look AHEAD aims to report outcome data on the success of the one-year intensive weight loss intervention and its impact on CVD risk factors such as diabetes control, lipids, blood pressure, and fitness.	(FY05) Information is not available regarding the impact of a one-year intensive weight loss intervention on these parameters in a similar diabetic population				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met — Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The target was met. Look AHEAD recruitment exceeded its target goal of 5,000 obese participants who have type 2 diabetes. In total, 5,145 participants were enrolled by May 2004. In addition, Look AHEAD exceeded its minority recruitment target by achieving approximately 37% minority representation from a range of backgrounds at 20 sites across the U.S. The study population was nearly 60% female, thereby meeting its gender recruitment target as well.

Each Look AHEAD participant is receiving either a more intensive lifestyle intervention program or a standard diabetes support and education program for 4 years, and the effect of this lifestyle intervention on the incidence of cardiovascular events is studied. Participants will be seen less frequently during an additional follow up period of 5 to 7.5 years, depending on the time of entry into the trial.

Implementation Strategy Advances or Other Highlights. The ACCORD trial has enrolled over 6,000 participants, which is 60 percent of the total eventual target of 10,000. The study is on target to complete participant enrollment by the end of June 2005. The participants are being randomized to receive either intensive glycemia treatment (HbA1c goal of <6%) or standard glycemia treatment (HbA1c goal of 7.0%-7.9%). About half of the participants are additionally randomized to be treated to a systolic blood pressure goal of <120 mmHg vs. a blood pressure goal of <140 mmHg; the other half are additionally randomized to be treated with a fibrate plus a statin vs. a statin alone. All participants are being followed to determine effects of the treatments on major cardiovascular events, defined as nonfatal heart attack, nonfatal stroke, or cardiovascular death. The study is performing well in achieving the treatment targets.

Minority recruitment in BARI 2D is outstanding. Sites with available minority populations are enrolling and retaining patients well above study goals. In addition, the diabetes management arm of the trial has been able to achieve hemoglobin A1c levels that are at or below the level recommended by the American Diabetes Association, and well below average for similar populations.

Recruitment for the Folic Acid for Vascular Outcome Reduction in Transportation (FAVORIT) trial began in July 2002. Participants are being randomized to receive either a multivitamin containing high doses of folic acid, vitamins B6 and B12 or one with no folic acid and the estimated average daily requirements of vitamins B6 and B12. As of August, 2004, a total of 2,000 study participants have been randomized into the trial.
In addition, in FY 2004 the NIH funded the "Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM)" randomized clinical trial. The study is not yet open for patient recruitment.

Efficiency. The Look Ahead recruitment target was ambitious and the recruitment effort vigorous. Look AHEAD had aimed to recruit (and randomize) 5,000 participants, but was able to recruit 5,145 overweight or obese individuals with type 2 diabetes at 20 separate sites comprising 16 centers across the U.S. and including a wide range of racial and ethnic populations.

PART

This goal was included in the FY 2006 PART of the Extramural Research Program. See Section C.1 to review results and recommendations.

SRO-6.3 BY 2012, DEVELOP A KNOWLEDGE BASE ON CHEMICAL EFFECTS IN BIOLOGICAL SYSTEMS USING A SYSTEMS TOXICOLOGY OR TOXICOGENOMICS APPROACH.

BACKGROUND

Disease Burden

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

NIH also seeks to implement international standard file format for data exchange, extend the database object model to include toxicology/pathology fields, and create a data portal that will load National Toxicology Program (NTP) and commercial Xybion toxicology data. This will create the capability to

import (and export) and link molecular expression data to animal effects data so as to evaluate global changes in gene and protein expression as a function of dose, time, and severity of toxic effect.

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

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

PERFORMANCE MEASURES		FY 2003	FY 2004	FY 20lis
Launch a pilot prototype database project to test the design and implementation of the knowledge base components and system architecture.	(FY02) Intramural databases and commercial software to build ProtoCEBS available	◆		
FY 03	*Actual Performance:* (MET) ProtoCEBS launched, tested, and implemented.			
Create the capability to import, export, and link molecular expression data by extending the Chemical Effects in Biological Systems (CEBS) database object model to include toxicology/pathology fields, and by creating a data portal that will load toxicology data.	(FY03) CEBS object model to capture molecular expression data (only) designed but not tested		◆	
FY 04	*Actual Performance:* (MET) CEBS now has a data portal that loads toxicology data. CEBS can import, export, and link molecular expression data to toxicology/pathology fields.			
Create and provide public access to a global molecular expression and toxicology/pathology database of environmental chemicals and drugs (CEBS), featuring simple query download capability.	(FY03) CEBS version 1.0 launched in August 2003 contains only microarray data		O	
	Actual Performance: Performance results will be reported in February 2006.			
Enhance the CEBS to allow facilitate integration of transcriptomics, proteomics, and toxicologic data for the same compound.	(FY04) The CEBS is limited to individual data sets and cannot integrate data from multiple data sets for a single compound			o
FY 06	*Actual Performance:* Performance results will be reported in February 2007.			

O Target Active • Target Met Target Extended ° Target Not Met

Summary of FY04 Performance Results

Target . The FY04 target was met because the CEBS now has a data portal that loads toxicology data. Functionally, this allows CEBS to import, export, and link molecular expression data to toxicology/pathology fields. It is capable of storing the basic description of a toxicogenomics study design, storing and analyzing microarray datasets developed using leading commercial platforms, and storing datasets representing toxicology/pathology outcomes.

Implementation Strategy Advances or Other Highlights. The CEBS System Biology object model (CEBS SysBio-OM) was completed to enable capture of multi-domain -omics datasets (e.g., transcriptomics, proteomics, and metabonomics). In addition, a capability was added to capture

information on the toxicogenomics study design and toxicology/pathology outcomes, which resulted in CEBS SysTox-OM.

SRO-7.1 BY 2005, EVALUATE 10 COMMONLY USED BOTANICALS FOR INHIBITION/INDUCTION OF ENZYMES THAT METABOLIZE DRUGS AS A METHOD OF IDENTIFYING POTENTIAL BOTANICAL-DRUG INTERACTIONS.

BACKGROUND

Prevalence/Incidence

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

Disease Burden

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH's strategic approach to fulfilling this goal is to provide continual support of solicited and unsolicited studies of botanicals and review investigator progress annually. In addition, under the National Toxicology Program (NTP), NIH will complete studies of goldenseal *(Hydrastis canadensis),* ginkgo *(Ginkgo biloba),* milk thistle *(Silybum marianum),* and grapeseed oil *(Vitis vinefera.)*. These strategies should lead to the discovery of additional botanical/drug

interactions. By 2005, NIH will complete evaluations of 10 commonly used botanicals for inhibition/induction of enzymes that metabolize drugs as a method of identifying potential botanical-drug interactions.

PERFORMANCE MEASURES	BASELINE					
Identify results of studies on three botanicals that show inhibition/induction of enzymes that metabolize drugs.	(FY02) Some characterization of St. John's wort; very little known about other botanicals					
Actual Performance: (MET) Effects were observed on selected botanical extracts on the inhibition or induction of selected enzymes that metabolize drugs.						
Identify results of studies on three additional botanicals that show inhibition/induction of enzymes that metabolize drugs.	(FY03) St. John's wort better characterized. Good characterization of ginkgo, garlic, saw palmetto, 2 species of ginseng, and PC-SPES		•			
Actual Performance: (MET) Effects were observed on three selected botanical extracts on the inhibition or induction of selected enzymes that metabolize drugs.						
Identify results of studies on four additional botanicals that show inhibition/induction of enzymes that metabolize drugs.	(FY03) Characterization of additional botanicals from FY 2004			o		
Actual Performance: Goal efficiently completed in 2004.						

O Target Active • Target Met — Target Extended ° Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target was met and the overall goal achieved one year early. The FY 2003 target was exceeded with a total of seven botanicals studied. Then in FY 2004, NIH studied an additional three botanicals for a total of ten. Thus, the goal was achieved one year early. The botanical studied in FY 2004 were: green tea, echinacea, and kava kava. During FY 2004, NIH researchers learned that when a decaffeinated extract of green tea was administered at a dose comparable to that in dietary supplements, no effects on either CYP2D6 or CYP3A4 were detected. Results of studies on echinacea were complex showing that its effect on CYP activity varied with the enzyme. Echinacea inhibited the CYP1A2 and CYP2C9 enzymes, thus delaying clearance of some medications, potentially allowing them to accumulate to toxic levels. Conversely, echinacea caused an increase in CYP3A enzyme activity, creating circumstances under which some medications could be eliminated before they could reach their therapeutic level. Studies on multiple constituents of kava kava showed that two compounds, desmethoxyyangonin and dihydromethysticin, markedly increase CYP3A23 and could cause the elimination of certain medications before they achieve a therapeutic concentration. This builds on previous studies showing kava's ability to increase the level of CYP3A4. Together, these studies illustrate the importance of examining the impact of commonly used botanicals on drug metabolism to prevent the possibility of adverse events such as toxicity or even death when botanicals and drugs are taken together.

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

- Donovan JL, et al. Green tea (Camellia sinensis) extract does not alter cytochrome P-450 3A4 or 2D6 activity in healthy volunteers. Drug Metab Dispos. 2004 Jun 9 [Epub ahead of print]
- Gorski JC, et al. The effect of echinacea (Echinacea purpurea root) on cytochrome P450 activity in vivo. Clin Pharmacol Ther. 2004 Jan;75(1):89-100.

- Ma Y, et al. Desmethoxyyangonin and dihydromethysticin are two major pharmacological kavalactones with marked activity on the induction of cytochrome P4503A23. Drug Metab Dispos. 2004 Jul 28 [Epub ahead of print].

Efficiency. This goal has been achieved sooner than planned. The researchers conducted targeted research and examined multiple botanicals according to their specific area of expertise, which facilitated greater results. The speed with which the researchers characterized the botanicals allowed the examination of three more than planned.

SRO-7.2 BY 2006, INTEGRATE NANOTECHNOLOGY-BASED COMPONENTS INTO A SYSTEM CAPABLE OF DETECTING SPECIFIC BIOMARKERS (MOLECULAR SIGNATURES) TO ESTABLISH PROOF OF CONCEPT FOR A NEW APPROACH TO THE EARLY DETECTION OF CANCER AND, ULTIMATELY, CANCER PREEMPTION.

BACKGROUND

Prevalence/Incidence

Cancer is the second leading cause of death in the United States. In 2004 an estimated 1,368,030 persons in the United States will be diagnosed with cancer, including 230,110 prostate cancers, 215,990 female breast cancers, 173,770 lung and bronchus cancers, and 146,940 cancers of the colon/rectum. These estimates do not include most skin cancers; new cases of skin cancer are estimated to exceed 1 million per year. Over two-thirds of all cases of cancer occur among people age 65 years and older.

Disease Burden

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

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

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

Rationale

Recent advances in understanding the molecular basis of cancer and the associated development of novel molecular technologies in areas such as proteomics, portend a future where cancer can be detected early and preempted before it spreads, perhaps on an individual basis. For example, nanoscience offers unparalleled opportunities to measure and monitor changes within cells at the level of multiple atoms. Applications of nanotechnology have the potential to shift the paradigm of cancer toward earlier detection and prevention and provide a new platform for eventual high-throughput diagnostics and, ultimately, real-time monitoring of patients.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To accomplish the goal of integrating nanoscale components into a system capable of detecting cancer at its earliest stage, NIH will first establish intramural and extramural collaborations to

develop, characterize, standardize and test nanoscale devices that are 10-200x smaller than human cells. Concomitantly, a new national Nanotechnology Characterization Laboratory will generate profiles of nanoparticles in biological systems; develop standards for nanodevices enabling researchers to develop cross-functional platforms; generate data to assist researchers in choosing a nanoscale device for a particular clinical or research application; and develop data to support regulatory sciences for the translation of nanotechnology into clinical applications.

In addition, NIH will use Broad Agency Announcements (BAAs) to identify critical technology platform needs and to develop technology programs that will create platforms for clinical application in cancer research.

PERFORMANCE MEASURES	BASELINE					
Establish intramural and extramural collaborations to select and employ substrate nanotechnology fabrication techniques to enable high-throughput and highly reliable/reproducible proteomic analyses.	(FY02) Lack of relevant collaborations					
Actual Performance: (MET) Collaborations established and work progressing on employing nanotechnology techniques to enable high-throughput proteomic analyses relevant to early detection of cancer.						
Establish a core laboratory at NIH to bring together extramural and intramural fabrication technologies with the capability to derive targets, identify the most promising applications for combined functionalized nanoparticles, and steward therapeutic nanotechnologies through validation.	(FY03) No current core laboratory with needed capacity					
Actual Performance: (MET) The national Nanotechnology Characterization Laboratory (NCL) has been established and will enable development of essential data about the profiles of nanoparticles in biological systems.						
Integrate nanosensors and nanoparticles into a platform technology for development in applied research settings.	(FY03) Existing nanosensors and nanoparticles not integrated into a common platform			o		
Actual Performance: Performance results will be reported in February 2006.						
Integration of nanotechnology-based components into a system capable of detecting biomarkers *in vitro*.	(FY04) Nanocantilevers, nanowires, and nanochannels currently in development, but not yet tested for cancer detection, imaging, and treatment *in vitro*				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met -> Target Extended ° Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target has been met because the national Nanotechnology Characterization Laboratory (NCL) has been established. The primary goal of the NCL is to characterize nanomaterials intended for cancer diagnostics and therapeutics. The NCL will therefore adopt a 'systems approach' model to meet end-user requirements. End-users of the characterization data are cancer researchers, the FDA, and the pharmaceutical industry.

The NCL is adjacent to, and will integrate with, other relevant Frederick laboratories such as the peptide synthesis lab and the animal care facility. This laboratory includes: a tissue culture room, an isotope lab, two research bays, a cold room, a chromatography and electrophoresis area, and open floor space for the free-standing instrumentation and equipment necessary for the in vitro characterization of

nanomaterials. The NCL will enable development of essential data about the profiles of nanoparticles in biological systems. Because nanotechnology is a new field, there are few standards and limited physical and biological characterization reference data for identification of nanodevices potentially suitable for a given clinical or research application making this a necessary step in the accomplishment of this goal.

A laboratory director, an immunologist, a toxicologist and a cell biologist to staff the NCL have been recruited. These scientists will initiate set-up of the laboratory, work with FDA and the cancer nanotechnology working group, and begin biological characterization of nanotechnology devices.

Implementation Strategy Advances or Other Highlights. The Alliance for Nanotechnology in Cancer was created to integrate nanotechnology into the discovery, development, and delivery aspects of cancer research. In addition, a working group comprised of NIH staff, FDA staff, NIST staff, and extramural researchers has been meeting to coordinate nanotechnology research and development across NIH, as well as between NIH and other federal agencies.

A Memorandum of Understanding (MOU) with the National Institute of Standards and Technology (NIST) to accomplish the physical characterization of nanomaterials has been established. In addition, a contract with an extramural nanofabrication laboratory was awarded to provide rapid access to engineered nanoparticles for detection, molecular targeting, and drug delivery.

Efficiency. In 2003, no current core laboratory with needed capacity existed. To achieve GPRA SRO goal 7.2 in 2006, the NCL had to be completed expeditiously. As of June 2004, all planning, design, and renovation activities were complete. Recruitment of key personnel, including the director and supporting biologists, was completed in August 2004.

PART

This goal was included in the FY2006 PART of the Extramural Research Program. See Section C.1 to review results and recommendations.

SRO-7.3 BY 2005, CREATE THE NEXT-GENERATION MAP OF THE HUMAN GENOME, A SO-CALLED HAPLOTYPE MAP ("HAPMAP"), BY IDENTIFYING THE PATTERNS OF GENETIC VARIATION ACROSS ALL HUMAN CHROMOSOMES.

BACKGROUND

Prevalence/Incidence

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

Disease Burden

A major goal of genetic research is to identify gene variants that contribute to disease. Finding these variants allows an understanding of the disease process, thus enabling development of methods for disease prevention and treatment. For single-gene disorders, diseases like Huntington disease or cystic fibrosis with a relatively straightforward genetic basis, current methods have been highly successful in locating the genes involved. Most people, however, do not have single-gene disorders but develop common diseases such as diabetes, cancer, hypertension, heart disease, and psychiatric disorders, which occur because of interactions of multiple genetic and environmental factors. Strategies that work well

for single-gene disorders lack the power to map such "polygenic" disorders; thus, relatively little is known about the genetic basis of these common diseases or the factors that determine individual risk of disease, clinical course, or response to treatment.

Rationale

Sites in the genome where individuals differ in their DNA spelling by a single letter are called single nucleotide polymorphisms (SNPs). Recent work has shown that about 10 million SNPs are common in human populations. SNPs are not inherited independently; rather, sets of adjacent SNPs are inherited in blocks. By understanding the way in which genetic variations are correlated in these DNA "neighborhoods" or "haplotypes," considerable savings in time, effort, and cost can be achieved in uncovering the hereditary factors in disease. Although a region of DNA may contain many SNPs, it takes only a few SNPs to uniquely identify or "tag" each of the haplotypes in the region. This presents the possibility of a major shortcut in identifying hereditary factors in disease.

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

NIH has taken a leadership role in the development of the HapMap, a catalog of the haplotype blocks and the SNPs that tag them. The HapMap is a tool that can be used by researchers studying many diseases to find the gene variants that contribute to those diseases. HapMap will be a description of the patterns of human genetic variation. It will be a tool that researchers will use to find genes and genetic variations that affect health and disease. The HapMap will reduce the number of SNPs required to examine the entire genome for association with a phenotype from the 10 million SNPs that exist to roughly 200,00-500,000 tag SNPs. This will make genome scan approaches to finding regions with gene variants that affect disease risk much more efficient and comprehensive, since efforts will not be wasted typing more SNPs than necessary, and all regions of the genome can be included. In addition to its use in studying genetic associations with disease, the HapMap should be a powerful resource for studying the genetic factors contributing to individual variation in response to environmental factors, in susceptibility to infection, and in effectiveness of, and adverse responses to, drugs and vaccines. This new tool will thus allow researchers to study how disease processes work, which will lead to interventions to prevent, delay, or cure diseases.

Despite the progress this map will enable, it will be difficult to quantify fully the impact of the HapMap for some 5-10 years beyond its completion. During that time, it will be possible, however, to quantify how much the HapMap data are used, and to monitor the diseases and other phenotypes that will be studied using the HapMap.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To conduct the HapMap project, NIH organized an international consortium of researchers in Canada, China, Japan, Nigeria, the United Kingdom, and the United States, including eight genotyping research groups, five data analysis groups, a data coordination center, and four sample collection groups. The consortium had originally planned to identify an additional 3 million new SNPs needed to fill in areas where the current density of SNPs in public databases is not sufficient, but due to advances in technology the project has already identified a total of 6 million new SNPs. The consortium is collecting samples from four populations (CEPH [U.S. residents with ancestry from Western and Northern Europe], Yoruba in Nigeria, Chinese, and Japanese). The consortium is also developing scientific strategies to choose which SNPs to

study and how best to assess the quality of the data and derive haplotypes from the SNP data.

The genotyping research groups had originally planned to genotype about 1.6 million SNPs to discover the pattern of variation among the samples, but due again to improved technology, the team will now be able to study many more SNPs. The data from this effort will contribute greatly to the development of the HapMap. These genotype data will be analyzed to derive haplotypes, develop the HapMap, and then to identify a "gold standard" set of SNPs that contain most of the information on the patterns of genetic variation, thus making the HapMap maximally useful and efficient for later studies relating genetic variation to health and disease. Review of available SNPs has already demonstrated that the haplotypes in the Yoruba samples are shorter and therefore will require a denser SNP map.

PERFORMANCE MEASURES	BASELINE				
For existing blood samples from U.S. residents of Western and northern European ancestry, obtain additional consent from the donors for this new use and begin genotyping 300,000 single nucleotide polymorphisms (SNPs, sites in the human genome where individuals differ by a single letter) in those samples.	(FY02) 90 existing samples, none of which included the necessary consent for genotyping				
Actual Performance: (MET) All needed consents obtained and genotyping performed on 132,000 SNPs.					
Collect samples from populations in Japan, China, and Nigeria; complete collection of additional 3 million SNPs and release in public databases.	(FY03) 2.4 million SNPs in database				
Actual Performance: (MET) Sample collection has been completed, and greater than 3 million SNPs have been released in the public database.					
Develop a first-pass draft HapMap containing 600,000 SNPs.	(FY03) 2.4 million SNPs in database but none of the samples genotyped to produce any part of the HapMap			o	
Actual Performance: Performance results will be reported in February 2006.					

O Target Active **•** Target Met **—** Target Extended **X** Target Not Met

Summary of FY04 Performance Results

Target. NIH has met and greatly exceeded the target to collect and publicly release 3 million additional SNPs. Collection of samples from populations in China, Nigeria and Japan has been completed.

Implementation Strategy Advances or Other Highlights. The consortium had originally planned to identify an additional 3 million new SNPs to fill in areas where the current density of SNPs in public databases is not sufficient, but has greatly exceeded that number, having identified a total of 7.8 million new SNPs. The consortium has collected samples and consent from 270 individuals from four populations (CEPH [U.S. residents with ancestry from Western and Northern Europe], Yoruba in Nigeria, Chinese, and Japanese) whose DNA samples will be used for genotyping.

Efficiency. NHGRI was able to increase efficiency due to improved technology and sequenced 4.8 million additional single nucleotide polymorphisms (SNPs) across the genome for a total of 7.8 million SNPs. Additional SNPs were obtained in several ways: by whole genome and whole chromosome shotgun sequencing from Whitehead Institute and the Baylor College of Medicine, the Sanger Institute

in the United Kingdom, and from Applied Biosystem Inc., and were compared with the reference sequence to identify SNPs. These SNPs are all of high quality. As a result of advances in genotyping technology, NHGRI has been able to increase genotyping efficiency. High quality genotyping was performed at a cost of about 1 cent per genotype, substantially lower than when HapMap was begun in 2002.

SRO-8.1 BY 2007, DETERMINE THE GENOME SEQUENCES OF AN ADDITIONAL 45 HUMAN PATHOGENS AND 3 INVERTEBRATE VECTORS OF INFECTIOUS DISEASES.

BACKGROUND

Genomics, the science of deciphering and drawing information from the genetic code of an organism, is a powerful tool that NIH is using to understand the microbes that cause disease and design strategies to overcome them. With microbe-specific genome information, drugs can be targeted to specific genes, and the products of specific genes can be incorporated into experimental vaccines. Furthermore, strategies can be devised to counteract genetic mutations that cause a microbe to become drug resistant. Moreover, genetic variations detected in different strains of the same pathogen can be used to study the population dynamics of these strains. Recognizing the enormous potential of microbial genomics research, NIH has made a significant investment in the large-scale DNA sequencing of the genomes of human pathogens and invertebrate vectors of disease, including microorganisms considered to be potential agents of bioterrorism.

Rationale

Genomic information will aid in the identification of gene products critical to growth and pathogenicity of microbes and their vectors; these may serve as targets for new therapeutics, vaccines, and diagnostics. Significant progress in DNA sequencing technology has allowed genomic DNA to be sequenced more efficiently and cost-effectively. A critical companion to state-of-the-art DNA sequencing techniques are the bioinformatics, computational tools, and databases that provide the scientific community with the needed resources to query, analyze, and annotate the sequencing data and assemble genomes.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

In FY 2004, NIH will launch the NIAID Proteomic Centers. Proteomics is the study of all or large groups of proteins in cells, tissues, and organs and how they respond, interact, and change. This initiative will develop and enhance innovative proteomic technologies and methodologies and apply them to the understanding of the pathogen and/or host cell proteome (all proteins in cells, tissues, and organs) for the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics, and immunotherapeutics against microorganisms considered agents of bioterrorism.

In FY 2004, NIH will continue to support several activities to provide comprehensive genomic, bioinformatic, and proteomic resources to the research community for basic and applied research to rapidly address the Nation's biodefense needs. Activities to be expanded include: (1) the NIH Microbial Genome Sequencing Centers, (2) the Bioinformatics Resource Centers, and (3) the NIH-supported Pathogen Functional Genomics Resource Center.

PERFORMANCE MEASURES			2004				

PERFORMANCE MEASURES	BASELINE					
Complete the genomic sequences for at least five bacteria and two protozoan parasites that cause infectious disease.	(FY02) Genome sequences for 32 bacterial pathogens, 1 protozoan parasite, and 1 insect completed					
Actual Performance: (MET): Genomic sequences were identified for 8 bacterial pathogens and 3 protozoan parasites						
Complete the genomic sequences of at least five bacterial pathogens, two protozoa, and three fungal pathogens that cause infectious disease.	**(FY03) Genome sequences for 40 bacterial pathogens, 4 protozoan parasites, and 1 insect completed**		•			
Actual Performance: (MET) Genomic sequences were identified for 18 bacteria, 4 protozoan parasites, and 3 fungi.						
Complete the genomic sequences of at least five bacterial pathogens, four protozoa, two fungal pathogens that cause infectious disease.	(FY04) Genome sequences for 58 bacterial pathogens, 8 protozoan parasites, 3 fungi and 1 insect completed			o		
Actual Performance: Performance results will be reported in February 2006.						
Com plete the genome sequence of at least six bacterial pathogens, two protozoan parasites, one fungal pathogen, and one invertebrate vector of infectious diseases.	(FY05) Genome sequences for 63 bacterial pathogens, 12 protozoan parasites, 5 fungi, and 1 invertebrate vectors of infectious diseases completed				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met -> Target Extended ° Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target was met and exceeded. Genome sequencing projects of 18 bacterial pathogens, four protozoan parasites, and three fungal pathogens were completed, largely due to advances in molecular biology that have led to remarkably fast and accurate methods for sequencing genomes. Briefly, 18 (rather than five) bacterial pathogen sequencing projects were completed in FY 2004, including *Bacillus anthracis* (four strains), *Bacillus cereus, Legionella pneumophila, Mycobacteria smegmatis,* another strain of *Clostridium perfringens, Candida albicans, Treponema denticola, Prevotella intermedia, Fusobacterium nucleatum, Actinomycetes naeslundii, Bacteroides forsythus, Streptococcus gordonii, Streptococcus mitis, Streptococcus sanguis and Streptococcus sobrinus*. DNA sequencing projects for parasites *Cryptosporidium hominis, Entamoeba histolytica, Toxoplasma gondii,* and *Trypanosoma brucei,* and fungi *Aspergillus fumigatus* and *Cryptococcus neoformans* (two strains) were completed. In FY 2004, NIH supported 40 large scale DNA sequencing genome projects for microbial pathogens and invertebrate vectors of infectious diseases. New genome sequencing projects supported by NIH that commenced in FY 2004 include: *Aedes aegypti, Burkholderia mallei, Burkholderia pseudomallei, Culex pipens, Francisella tularensis, Histoplasma capsulatum,* Influenza virus, *Ixodes scapularis, Mycobacterium tuberculosis, Vibrio cholerae,* and *Yersinia pestis.*

Implementation Strategy Advances or Other Highlights. In FY 2004, NIH supported 40 large scale DNA sequencing genome projects for microbial pathogens and invertebrate vectors of infectious diseases. New genome sequencing projects supported by NIH that commenced in FY 2004 include: *Aedes aegypti, Burkholderia mallei, Burkholderia pseudomallei, Culex pipens, Francisella tularensis, Histoplasma capsulatum,* Influenza virus, *Ixodes scapularis, Mycobacterium tuberculosis, Vibrio cholerae,* and *Yersinia pestis.*

In FY 2004, NIH continued to support a diverse genomics research program that includes genome sequencing of potential bioterrorism microbes. NIH continued to collaborate with the Defense Advanced Research Products Agency (DARPA) to sequence such potential agents of bioterror as the bacteria that cause brucellosis, Q fever, gangrene, and epidemic typhus. In addition, NIH has continued to work with several international agencies and organizations to identify mechanisms for improved coordination of efforts and capitalization on the data accrued by these sequencing projects.

A second Microbial Genome Sequencing Center was established to allow for rapid and cost-efficient production of high-quality, microbial genome sequences. In addition, contracts were awarded to support a broad range of genomics and genomics-related research: Bioinformatics Resource Centers, Biodefense Proteomics Research Programs, and a Populations Genetics Analysis Program: Immunity to Vaccines/Infections. Also, NIH established an Influenza Genome Sequencing Project that will sequence the whole genome of many human and avian influenza viruses and provide influenza sequence data rapidly to the public domain.

Additional genomic resources, including protein expression clone sets and DNA microarrays were made available in FY 2004 through the NIH's Pathogen Functional Genomics Resource Center (PFGRC). The PFGRC has undertaken comparative genomic analyses to identify genetic variations and relatedness within and between species that define characteristic pathogen biosignatures that can be used for rapid and accurate pathogen identification in forensics and other applications.

Efficiency. Technological developments have resulted in a drastic decrease in the cost of sequencing DNA as well as a great increase in efficiency (the sequencing process has become faster and more accurate). For example, the Institute for Genomic Research (TIGR), an international microbial sequencing center, reported that sequencing a piece of DNA, approximately 650 nucleotides in length, decreased from $7.70 in 1996 to $0.98 in 2004. In FY 2004, these technological advances made possible completion of 25 pathogen genome sequencing projects, 15 more that the FY 2004 performance target.

SRO-8.2 **BY 2009,** IDENTIFY AND CHARACTERIZE TWO MOLECULAR INTERACTIONS OF POTENTIAL CLINICAL SIGNIFICANCE BETWEEN BONE-FORMING CELLS AND COMPONENTS OF BONE. SUCH INTERACTIONS ARE DEFINED AS THOSE HAVING SIGNIFICANT IMPACT ON THE ACCRUAL OF BONE MASS OR THE ACTUAL MECHANICAL PERFORMANCE OF BONE (I.E., FRACTURE RESISTANCE) IN LABORATORY ANIMALS.

BACKGROUND

Skeletal health depends on the process of bone turnover, in which small regions of bone are broken down (resorbed) and then replaced with new bone. The regulation of the balance between bone resorption and new bone formation, which can be affected by nutritional, endocrine, and pharmacological factors, is critical to maintaining bone mass and preventing fracture. An excess of resorption over formation underlies many bone diseases, such as postmenopausal osteoporosis. Osteoblasts are the cells that form new bone during bone turnover. In addition, some osteoblasts remain embedded in the bone, becoming osteocytes. Recent work has shown that osteocyte survival is an important requirement for skeletal health. Bone is composed of mineral crystals embedded in a matrix made up of many different proteins. There is evidence that interactions between matrix proteins and proteins found at the cell surfaces of osteoblasts and osteocytes produce signals that are important for the regulation of bone turnover and the survival of osteocytes. However, the molecular details of cell-matrix interactions have been explored in only a few instances. If known, the mechanisms of these

interactions could yield targets for new drugs that might act to stimulate bone formation or block bone resorption. Understanding how the number and activity of osteoblasts are controlled could lead to new therapies for restoring lost bone, either with drugs or by tissue-engineering approaches.

Rationale

It is clear from work to date that altering cell-matrix interactions can produce changes in bone remodeling activity and bone mass. However, before these findings can be translated into therapeutic applications, it will be necessary to refine our understanding of known cell-matrix interactions and identify new interactions with important roles in the maintenance of skeletal health. Recent advances, particularly in the genetic manipulation of mice, make it possible to define the function of different matrix proteins and the cell surface proteins that interact with them. For example, mice can be created that either lack a certain matrix protein or produce abnormally large amounts of the protein. Cell surface proteins thought to interact with matrix proteins also can be tested in this way. It is important to conduct these experiments with intact, genetically modified mice, in addition to cell cultures, for two reasons. First, although osteoblasts can be induced to produce bone matrix in culture, the interaction between cells and matrix in culture is not normal. For example, osteoblasts do not become osteocytes within the bone produced in culture. Second, the consequences of interfering with specific cell-matrix interactions can be assessed thoroughly by examining the bones of mice. This can even indicate the ultimate effect on the mechanical strength of the bones.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To date, nine relatively abundant proteins have been identified in bone matrix, in addition to collagen, the principal structural component of bone. Two of the non-collagen proteins, thrombospondin-2 (TSP2) and osteonectin, were selected for initial study, based on evidence that they play important roles in the generation and survival of osteoblasts. Studies have now also been initiated on three additional matrix proteins: fibronectin, dentin matrix protein-1 (DMP-1), and connective tissue growth factor (CTGF). Genetically modified mouse strains lacking these proteins have been generated. Using cells isolated from the genetically modified mice, cell culture systems have been developed, in which the effects of the matrix proteins on osteoblasts and their precursor cells can be determined. These mice and cell culture systems are valuable tools for the strategies outlined below.

NIH will use existing mouse strains and cell culture systems to (1) determine the effects of matrix proteins on the generation of osteoblasts from precursors and on the survival of the cells, (2) identify the biochemical pathways within cells that mediate the effects of the proteins, (3) identify the specific portions of the proteins that are responsible for the effects, and (4) identify the molecules on the surface of cells that interact with matrix proteins. This strategy is important to achieving this goal for several reasons. First, cell cultures allow for very precise measurements of biological effects, at low cost. Detailed knowledge of the effects of matrix proteins on isolated cells is the first requirement for predicting the effects of drugs that either mimic or block the cell-matrix interactions. Second, identification of the active portions of the matrix proteins and the interacting cell proteins will allow for design of new drugs and selection of existing drugs for testing. Third, observations of genetically modified mice place the results of cell culture experiments in the context of the intact organism. This is essential because therapies would be applied in intact humans, where many factors are present that cannot be replicated in cell cultures.

NIH will also employ genetic engineering technology to generate new mouse strains: (1) mice that allow for visualization of matrix proteins in tissue samples and (2) mice in which the matrix proteins are produced in certain cells, at specific stages of development. Using new mouse strains will help determine the effects of matrix protein-osteoblast interactions at different stages of osteoblast

development. This strategy adds to the information gained by the first strategy, placing the initial observations in the context of time and place. Knowing where and when the matrix proteins are produced in a normal mouse gives a rough idea of which cells must be targeted in designing a therapy and at what stage in cell development the effect is most critical. Producing the proteins at specific times and places by genetic technology establishes these parameters more precisely. Although mice wholly deficient in fibronectin are not viable, it may still be possible to selectively engineer osteoblasts to be deficient in this protein. If this ambitious target is successful, then it will be possible to dissect fibronectin's role in bone formation. Such information will have a direct relationship to successfully achieving the goal.

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

PERFORMANCE MEASURES	BASELINE					
Characterize effects of the bone protein thrombospondin-2 on the generation of bone-forming cells from precursor cells in the bone marrow and identify regions of the thrombospondin-2 molecule that are required for the effects.	(FY02) Information on the role of thrombospondin-2 in bone generation is incomplete.	•				
Actual Performance: (MET) Thrombospondin-2 promotes bone formation in the early stage of cell differentiation; functional elements at one end of molecule responsible for this effect.						
Identify biochemical pathways in bone-forming cells that are responsible for extended survival of cells on interaction with the bone protein osteonectin.	(FY03) Biochemical pathways that mediate cell survival are unknown		•			
Actual Performance: (MET) Results suggest that the interaction of bone-forming cells with osteonectin enhances cell survival through activation of the Wnt pathway.						
Identify regions of bone and bone marrow in which thrombospondin-2 is produced under conditions of bone loss and bone formation. Generate a genetically altered mouse strain in which a fluorescent protein is produced under the control of the same genetic elements that control the production of thrombospondin-2.	(FY03) Information incomplete on where thrombospondin-2 is produced; mouse model can provide this data			o		
Actual Performance: Performance results will be reported in February 2006.						
Generate a genetically modified mouse in which only bone-forming cells are deficient in fibronectin, and identify the cell surface molecule mediating interaction between bone-forming cells and connective tissue growth factor.	(FY04) Mice wholly deficient in fibronectin are not viable. Molecules interacting with CTGF are unknown				o	
Actual Performance: Performance results will be reported in February 2007.						

o	Target Active	•	Target Met		Target Extended	X	Target Not Met

Summary of FY04 Performance Results

Target. The target was met by testing three biochemical pathways and discovering that the activation of one - the Wnt pathway - was markedly decreased in mice cells that are deficient in the matrix protein osteonectin. Other work using this animal model, which exhibits decreased rates of bone formation and an accelerated loss of bone with age, showed that the Notch 1 and TGF-beta pathways were essentially normal.

This finding suggests that interaction of bone-forming cells with osteonectin enhances cell survival through activation of the Wnt pathway. Further, these data support the previous studies that established the Wnt pathway prevents cell death and prolongs cell survival in many types of cells. The Wnt pathway is the target of numerous on-going drug development efforts in both academic and for-profit settings. Identifying the cell-osteonectin interaction as one way of activating the Wnt pathway provides new clues to the types of molecules that might be pharmacologically useful.

Implementation Strategy Advances or Other Highlights. Additional work was carried out on matrix component biglycan, which has been shown to be essential for the action of bone morphogenetic protein 4 (BMP-4), a key stimulator of bone formation. Evidence suggests that biglycan functions to retain BMP-4 close to the surface of bone-forming cells, so that it can interact more readily with components of the cell surface. BMP-4 and related molecules are already used, particularly in surgical procedures, to stimulate new bone growth. The discovery of the role of biglycan in the action of BMP-4 could lead to methods for increasing the efficiency of BMP treatments and reducing their cost.

SRO-8.3 BY 2006, BUILD A PUBLICLY ACCESSIBLE COLLECTION OF REFERENCE SEQUENCES (REFSEQ COLLECTION) TO SERVE AS THE BASIS FOR MEDICAL, FUNCTIONAL, AND DIVERSITY STUDIES. A COMPREHENSIVE REFSEQ COLLECTION WILL SERVE AS A FOUNDATION FOR GENOMIC RESEARCH BY PROVIDING A CENTRALIZED, INTEGRATED, NONREDUNDANT SET OF SEQUENCES, INCLUDING GENOMIC DEOXYRIBONUCLEIC ACID (DNA), RIBONUCLEIC ACID (RNA) TRANSCRIPT, AND PROTEOME (PROTEIN PRODUCT) SEQUENCES, INTEGRATED WITH OTHER VITAL INFORMATION FOR ALL MAJOR RESEARCH ORGANISMS.

BACKGROUND

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

Rationale

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

computational and expert tasks must be ongoing so that (1) the collection stays current as new data become available, (2) quality is ensured, and (3) new opportunities that add value are identified.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

To facilitate more sophisticated and specialized uses of RefSeq, the database will be available for complete downloading to allow commercial or academic groups to generate value-added versions of the database to target specialized or species-specific audiences and allow them to perform exhaustive analyses across the entire data set. Through extended development of the suite of RefSeq analytic tools, NIH intends to increase by many times the number of scientists who will be able to carry out computationally sophisticated analyses on the RefSeq Collection without the need for programming skills.

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

PERFORMANCE MEASURES	BASELINE	FY 2004	FY 2008
Make the RefSeq Collection database available for downloading to enable commercial or academic groups to perform exhaustive analyses across the entire RefSeq Collection data set.	(FY02) At the end of FY02, the RefSeq collection included 446,000 proteins and was not available for FTP		
FY 03	*Actual Performance:* (MET) The RefSeq collection was made available on a regular release cycle to scientists at commercial and academic sites for downloading and analysis of the entire data set.		
Develop the infrastructure to support wider access to the RefSeq Collection via the Internet to provide users with a centralized set of annotated sequence information.	(FY03) RefSeq collection includes sequence data from 2124 species; only a limited database is available	e	
FY 04	*Actual Performance:* (MET) The RefSeq collection is now fully available via the online resource Entrez Gene.		
Expand the project to include outside groups to increase the amount of sequence and functional information in the database. Collaborations will provide additional reference sequence records, whole-genome annotation, functional annotation of multigene families, and expert review of single genes.	(FY04) About 40 collaborations in place for obtaining annotated RefSeq records and other functional data	o	
I	*Actual Performance:* Performance results will be reported in February 2006.		

O Target Active • Target Met — Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target was met by developing the database and software infrastructure to provide internet access to all records included in the RefSeq collection. The web resource Entrez Gene provides gene-oriented access to the RefSeq collection and includes descriptive information about genes including names, map information, representative sequence information, publications, disease associations, and extensive cross-linking to numerous other internet resources including those reporting expression and disease information. Accessibility of the RefSeq collection in the context of rich descriptive information significantly enhances information retrieval, discovery, and navigation.

The initial release of Entrez Gene in December 2003 includes the RefSeq collection, however, it did not provide support for all areas including FTP. Additional areas of descriptive information were added incrementally in FY 2004 including a significant expansion in representing conserved protein domain data and in providing an annotated bibliography known as Gene References into Function, or GeneRIFs. Representation of Entrez Gene data for FTP downloads has also been expanded incrementally during this time period.

Implementation Strategy Advances or Other Highlights. To generate an internet based access to the full RefSeq collection, databases, software, and a series of processing steps were developed. The database content is updated regularly to reflect additions or other changes in the RefSeq collection. RefSeq records may be available for several weeks prior to loading them into Entrez Gene due to asynchronous processing schedules. In addition, the infrastructure was developed to support adding supplementary information including the GeneRIF annotated bibliography.

RefSeq and other data loaded to Entrez Gene are subject to a quality control procedure to detect errors and conflicts. Documentation was written and is available on the Entrez Gene web site. In addition, users can subscribe to an email announcement service to receive notices of changes and addition of new types of supplementary data.

The table below shows the growth of RefSeq and Entrez Gene.

RefSeq Growth:

TIME FRAME	NUMBER OF SPECIES	NUMBER OF RECORDS	NUMBER OF PROTEINS
As of October 2002	Not tracked	Not tracked	446,000
As of October 2003	2124	1,097,404	831,287
As of October 2004	2645	1,709,723	1,218,266

Entrez Gene Growth:

TIME FRAME	NUMBER OF SPECIES	NUMBER OF RECORDS
As of October 2003	Resource not available	Resource not available
As of December 2003	1,982	708,846
As of October 2004	2,491	1,071,343

Efficiency. The RefSeq project has met FY04 milestones over 5 months early through the deployment of a centralized Web site that provides access to the full RefSeq collection as well as a file transfer (FTP) facility for users to create their own local copies of the collection. The availability of the RefSeq collection in Entrez Gene facilitates access of RefSeq records and curated descriptive information. This enables thousands of US scientists to use their valuable research time more efficiently.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

The RefSeq project has met FY04 milestones over 5 months early through the deployment of a centralized Web site that provides access to the full RefSeq collection as well as a file transfer (FTP) facility for users to create their own local copies of the collection. As of April, 2004, the RefSeq collection included 977,458 proteins and 2,395 species. Also, RefSeq has begun work on FY05 targets by establishing collaborations with several genome-specific working groups (see www.ncbi.nlm.nih.gov/RefSeq/collaborators.html for list of over 20 collaborations). These groups have assisted in defining new genes, in adding functional content, and updating RefSeq records. A genome project database is being developed to track these collaborations in conjunction with genome-level sequencing projects, and to identify data sources and individual experts on specific genes and gene families. Software has been developed (Genome Workbench) that will facilitate electronic collaboration with genome working groups. A major development in accelerating progress in the rate of data incorporation has been the initiation of R&D contracts and licensing arrangements which will permit the incorporation of existing gene annotation databases in the RefSeq project. The aggregate number of records from these databases exceeds 25,000. Participants include the Online Mendelian Inheritance in Man (Johns Hopkins), Gene Review (University of Washington), and the Human Protein Reference Database (Johns Hopkins). Also, expert reviews of single genes or gene families are being facilitated through electronic authoring in the NCBI Electronic Monograph series. Although none of these activities can be reported as complete at this time, progress is proceeding faster than expected; consequently, no FY06 target is needed.

SRO-8.4 BY 2009, ASSESS THE IMPACT OF TWO MAJOR INSTITUTIONAL DEVELOPMENT AWARD (IDEA) PROGRAMS ON THE DEVELOPMENT OF COMPETITIVE INVESTIGATORS AND THEIR CAPACITIES TO COMPETE FOR NIH RESEARCH FUNDING.

BACKGROUND

The Institutional Development Award (IDeA) Program was authorized by the NIH Revitalization Act of 1993 to foster health-related research and increase the competitiveness of investigators at institutions located in States with historically low grant awards from NIH. An institution's eligibility to participate in the IDeA Program is determined by the aggregate level of NIH grant funds collectively received by all research institutions within its State over the preceding consecutive 5-year period and/or the average success rate of research applications over that same time span. In FY 2004, States that received on average less than $100 million in NIH grant awards and/or had a success rate of less than 20 percent during FY 1999 - 2003 were eligible for the IDeA Program.

The IDeA Program was established in FY 1993 at a funding level of $750,000, which slowly increased to $10 million in FY 1999. This limited funding precluded development of major initiatives. However, in FY 2000, funding increased to $38.5 million, which allowed for the development and implementation of a more comprehensive initiative, the Centers of Biomedical Research Excellence (COBRE). The COBRE initiative was specifically designed to enhance the pool of well-trained

investigators who could successfully compete for NIH grant awards. This initiative augments and strengthens institutional biomedical research capacities by expanding or modifying research facilities, equipping laboratories with modern research equipment, providing mentoring for promising candidates, and developing research faculty through support of a multidisciplinary center, led by a peer-reviewed, funded investigator with expertise central to the research theme of the center.

The FY 2001 appropriation for the IDeA Program increased to $100 million and this allowed for the development of a second initiative, the Biomedical Research Infrastructure Network (BRIN). BRIN enhances the pipeline for outstanding students and bolsters the quality of science faculty at baccalaureate and other participating institutions. The BRIN is intended to network research intensive and undergraduate institutions in IDeA states to prepare students for graduate and professional schools as well as for careers in the biomedical sciences. In FY 2004, BRIN was renamed IDeA Networks of Biomedical Research Excellence (INBRE) to better reflect the purpose of the program and to avoid confusion with another program with a similar name.

In FY 2004, the appropriation for the IDeA Program was $214 million. It is anticipated that future funding will remain at or above this level.

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

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

Since the COBRE began before INBRE, the two evaluations will be conducted at different intervals. The evaluation design study for COBRE will be completed in FY 2004 and that for INBRE will be completed in FY 2005. It is anticipated that the full-scale evaluation for COBRE will begin in FY 2006 and be completed in FY 2008. The full-scale evaluation for INBRE is anticipated to begin in FY 2007 and be completed in FY 2009.

The purpose of each evaluation design study will be to determine the best strategy for evaluating the program. Consideration will be given to determining the indicators that optimally assess whether the

research competitiveness and research capacity of the institutions has increased. Some target indicators have been proposed:

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

Further, the annual progress reports that collect potential indicator data will be used to validate the list of indicators developed through the evaluation design study. Whether or not these indicators should be measured at the state, institutional, and/or center level will be determined by the design studies.

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

PERFORMANCE MEASURES	BASELINE					
Develop a data collection and management system to allow for the retrieval of potential target indicators to evaluate the impact of the IDeA/Centers of Biomedical Research Excellence (COBRE) Program.	(FY02) Indictors from Pre-COBRE analysis and previous evaluations.	•				
Actual Performance: (MET) Data collection and management system in place for retrieval of potential target indicators related to evaluating impact of IDeA/Centers of Biomedical Research Excellence Program.						
Assessment Methodology for IDeA Program (Step 1): • Complete evaluation design to HAtpmiinp *n* r>r»nfinnpH lief *rtT* f^it-rvi^f indicators to measure IDeA/COBRE impact. • Develop a data collection system for BRIN.	(FY03) Data collection and management system to evaluate impact of IDeA/COBRE in place. (FY04) Indicators from IDeA/COBRE evaluation design.		•			
Actual Performance: (MET) The COBRE evaluation design, which includes a confirmed list of target indicators, is complete. Data collection and management system is in place for BRIN.						
Assessment Methodology for IDeA Program (Step 2): • Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/BRIN impact. • Assess results of COBRE evaluation design study.	(FY04) Data collection and management system to evaluate impact of IDeA/BRIN in place. (FY04) COBRE evaluation design completed but not evaluated.			o		
Actual Performance: Performance results will be reported in February 2006.						
Full-Scale Assessment of the IDeA Program (Step 1): • Initiate the full-scale evaluation for IDeA/COBRE.	(FY04) COBRE evaluation design				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active **•** Target Met Target Extended **X** Target Not Met

Summary of FY04 Performance Results

Target. The target was met by (1) completing the IDeA/COBRE evaluation design and (2) designing, testing, implementing, and launching a data collection and management system for BRIN.

The IDeA/COBRE final report included a confirmed list of target indicators that were separated into intermediate and long-term goals. Examples of intermediate indicators include: scientific publications, applications for NIH research grants, success competing for NIH research grants, research facilities and support services, students, science faculty, and permanent research positions in COBRE departments and high retention of COBRE investigators. Long-term indicators include: applications for research grants, especially RPGs, success competing for research grants, especially RPGs, degrees awarded in scientific fields, high retention of COBRE investigators and increase in the proportion of total NIH funding received. The success of this program, as demonstrated by the indicators, will serve as a building block toward increasing the research potential of the Nation.

The BRIN database captures the following potential target indicators: number of presentations, publications, NIH grant submissions and awards, other grant submissions and awards, recruited faculty, research personnel and research administrative staff members, and amount of newly constructed laboratory space. This database will be used to monitor the IDeA Program's progress toward increasing the capacities of institutions to conduct research.

Implementation Strategy Advances or Other Highlights. To assist in measuring the impact of IDeA/COBRE on the development of competitive investigators and their capacities to compete for NIH research funding, two contracts have been put in place. One contract deals with design and maintenance of a data collection and management system; the second focuses on conducting an initial COBRE evaluation design, which will identify the data needed to conduct the IDeA/COBRE full-scale evaluation. Using the database, NIH will be able to confirm the validity of potential target indicators needed to determine their impact on research competitiveness and research capacity.

SRO-8.5 BY 2009, DEVELOP AN ITEM BANK AND COMPUTERIZED ADAPTIVE TESTING SYSTEM AVAILABLE TO CLINICAL RESEARCHERS TO IMPROVE ASSESSMENT OF NON-SPECIFIC SYMPTOMS (e.g., PAIN AND FATIGUE) AND OTHER DOMAINS OF HEALTH-RELATED QUALITY OF LIFE IN CHRONIC DISEASE.

Background

Conventional clinical and functional measures of disease status do not fully capture the ways in which chronic diseases and their treatment affect individuals. Many aspects of patients' subjective experience, such as symptom severity and frequency, emotional and social well-being, and perceived level of health and functional ability are important targets for disease intervention that are not measured by x-rays or laboratory results. Measurement of patient-reported outcomes (PROs) is particularly important in clinical trials, where changes in clinical measurements or imaging results alone may not translate into important benefit to the patients, or in trials in which two treatments may be comparable in limiting or curing disease but have different adverse effect profiles differentially affecting symptoms, functioning, or other aspects of patients' quality of life.

The last several decades have seen a proliferation of tools to measure symptoms, quality of life, functional status, emotional status, and general perception of health. Although many of these instruments have good demonstrated reliability and validity, there are many limitations to current measurement approaches. One critical disadvantage is the inability to compare results across different studies when different measurement tools are used. These instruments may have non-comparable or non-combinable scores because each scale may use a different number of items, different response options, different reference periods, or different item content. For example, progress in clinical pain research is slowed by the use of various pain measurement scales that are not directly comparable. The length and complexity of questionnaires and batteries can also be problematic, creating a level of

respondent burden that hampers recruitment, results in too much missing data, or is detrimental to response validity and reliability. The clinical outcomes research enterprise would be enhanced greatly by the availability of a psychometrically validated, dynamic system to measure PROs efficiently in study participants with a wide range of chronic diseases and demographic characteristics.

Rationale

Increased availability of more precise, efficient and easier to use measures of quality of life and symptom indices will significantly facilitate all forms of clinical research and enhance patient care delivered on the front lines. The development of better health-related quality of life (HRQOL) and symptoms instruments would provide the needed tools for comparing the outcomes of preventive, rehabilitative, and curative interventions.

A new enabling technology, computerized adaptive (or dynamic) health assessments, can yield a more efficient and easier to use set of validated clinical research tools. Two critical concepts form the basis of this new technology. The first is that by collecting a large set of questionnaire items in subjects with the widest possible range of severity of disease and levels of health, one can construct reliable models (i.e., item response theory models) that predict the probability of specific responses by patients based on their answers to initial questions. The second concept uses software programs to control the specific set of questions asked of each patient. Based on the answers to initial questions, the program can focus the remaining questions to more accurately assess the patient's level of functioning. If these standardized instruments and information on their performance in reference populations were widely available, clinical researchers would be able to measure clinical outcomes far more accurately, compare across diseases or populations, account for co-morbid conditions, and ascertain the impact of nonspecific symptoms like fatigue, without the necessity of conducting or having to duplicate, previous validation efforts.

Properly constructed, this repository and supporting technology will lead to more efficient, precise and reliable assessment of quality of life and non-specific symptoms in clinical research, increasing the interoperability of clinical research, permitting the direct comparison of results even from different instruments, using different questions.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A multi-disciplinary network of cooperative agreements (PROMIS) will be funded to develop an item bank, test item response theory models of item performance, and develop a computerized adaptive testing system to measure a select number of health-related quality of life (HRQOL) domains and non-disease specific symptoms in patient with chronic illnesses. In FYs 05 and 06, the network will characterize the ability of commonly used instruments to capture these domains. The strengths, deficiencies, gaps, and redundancies in the most common instruments for these domains will be described. Network experts will guide the process of developing a set of items to be tested, some new and some from existing instruments, with input from patients. Data collection using this item set will be initiated in a wide range of patients suffering chronic diseases and conditions.

PERFORMANCE MEASURES	BASELINE		FY 2004		
Identify specific domains to be measured, evaluate existing measures and items, and develop instrument(s) and assessment methods for use in diverse chronic disease patient samples.	(FY04) Highly valid, reliable, and broadly usable assessment tools are needed to enhance clinical research on patient-reported chronic disease outcomes.			0	
FY 1 05 *Actual Performance:* Performance results will be reported in February 2006.					

Initiate administration of instrument(s) to a large, demographically diverse patient sample representing a wide range of chronic disease type and severity.	(FY05) An initial item pool for assessing specified domains of symptoms and/or domains of health-related quality of life developed using FY 05 target.	O	
	Actual Performance: Performance results will be reported in February 2007.		

O **Target Active** • **Target Met** — **Target Extended** **X** **Target Not Met**

Summary of Performance Results

Target. Performance will be reported in 2006.

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).

BACKGROUND

Disease Burden

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

Rationale

The premise of this goal is that targeted research on these topics will have a significant impact on the overall reduction of years lost to disabilities (YLDs) associated with depression in two ways. First, although effective treatments benefit millions of persons with major depression, a significant proportion (50%) of persons are not helped or do not fully recover when given a standard pharmacological or psychosocial intervention. 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 effective depression treatments are currently available, only an estimated 20 percent of patients obtain adequate treatment. Rates of underutilization are higher for persons of color, elderly persons, youth, and young and middle-age males. Although several models of care have proven effective in delivering adequate depression treatment, the uptake and maintenance of these patterns of delivery of care remain poor.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Several strategies are planned. NIH will investigate basic mechanisms underlying depression that may serve as important targets for intervention, such as the role of vascular changes in aging towards development of depression. Research will improve upon the definition and assessment of depression treatment outcomes and identify predictors of treatment response at various points throughout the course of illness. NIH plans to test interventions that produce longer recovery periods for those most at risk for relapse in community populations, such as the elderly. Research will identify factors that have an impact on effective and sustainable dissemination and implementation of scientific findings at multiple environmental levels. Finally, NIH anticipates identifying the mechanisms and processes by which depression has a relatively large influence on the course or outcome of a comorbid disorder associated with disability or premature mortality.

PERFORMANCE MEASURES	BASELINE					
Identify at least one biological (gene-environment) interaction that has high probability of contributing to depression.	(FY02) Known that stress linked to depression but interaction not known	•				
Actual Performance: (MET) A link was made between a specific gene-environment interaction (5-HTT and high stress) and vulnerability to depression.						
Determine whether vascular changes related to aging contribute to depression.	(FY03) Subcortical lesions, common in elderly with depression and in vascular disease, are being studied as potential cause of depression		•			
Actual Performance: (MET) A strong correlation has been found between vascular changes resulting in unique lesions in the brain and depression in elderly patients.						
Determine at least four characteristics that help identify subgroups of people with depression who respond differentially to existing treatments.	(FY04) A series of clinical trials are currently underway that match patients' responses to different treatments			o		
Actual Performance: Performance results will be reported in February 2006.						
Identify at least one effective strategy for treating depression in the elderly in a variety of settings.	(FY05) A number of interventions to treat depression in the elderly are currently being developed and tested				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met — Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target has been met because of significant progress being made in understanding the potential links between vascular disease and depression in aging individuals. Mounting evidence indicates existence of a depression syndrome unique to elderly patients who have suffered from ischemic lesions in the connecting bundle of fibers called white matter that is found beneath the

cerebral cortex. These patients suffer from a type of depression that differs in clinical presentation from those of depressed individuals without such lesions. For example, they are significantly more likely to report a later age of depression onset, have a history of hypertension, and exhibit lassitude (difficulty in getting started or slowness in initiating and performing everyday activities.) Because of the unique nature of this form of depression, it has been proposed that the term "subcortical ischemic depression" be used to describe it.

Research in the past year has made great strides in elucidating the nature of subcortical ischemic depression. The use of functional magnetic resonance imaging (fMRI) has demonstrated that these unusual lesions appear as "bright spots" or hyperintensities in the subcortical white matter and are found in higher numbers in depressed patients. These patients also tend to be hypertensive, signifying the involvement of vascular abnormalities. Complimentary work on postmortem brain samples is confirming this hypothesis, in that preliminary work has shown that depressed subjects' brains have unusually large blood vessels in the white matter regions associated with the hyperintensities seen in the neuroimaging studies. These findings will lead to further work designed to elucidate on a cellular level the reason for these vascular abnormalities, and ultimately to develop better treatments and preventive measures for this unique form of depression in the aged.

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

Major depression is associated with significant changes in neuroendocrine and autonomic activity. Such changes can place depressed people at increased risk for physical diseases. Conversely, some physical diseases may contribute to the onset of depression. Investigators are using various approaches to study the mechanisms involved: imaging studies examine whether decreased flow of blood to specific areas of the brain may be a risk factor for late-life depression; other studies explore the possibility of chronic stress causing atrophy in the hippocampus (memory center) and the effect of stress on the vascular and immune systems; prevention clinical trials test patients at risk for depression (e.g., coronary artery bypass patients) to determine whether early drug treatment forestalls the development of postsurgical depression; and treatment trials study patients with comorbid conditions (a physical illness and depression) to determine which specific classes of drugs and/or psychosocial therapies are most effective for which comorbid diseases.

NIH is funding several large multi-site clinical trials to help answer these treatment questions. For example, one long-term study will help decide which treatments work best for major depression if the first medication does not produce an acceptable response. Other trials will help establish whether genetic factors account for differences in response to medications in various subpopulations. Another study focuses on how best to treat adolescents who fail to respond to the first antidepressant medication they have tried and includes a test group receiving cognitive behavioral therapy combined with medications. The overall goal is to develop customized treatments that will enable durable recovery from depression. Depression is very common in Parkinson's Disease (PD) patients, causing increased disability, lower quality of life, and increased caregiver burden. Antidepressant medications are often used to treat these patients, but their efficacy, safety and tolerability in PD patients has not been

established. NIH is funding multiple studies on the short and long term use of antidepressants and other interventions in PD patients in order to better inform their clinical treatment for depression.

SRO-9.2 BY 2010, IDENTIFY CULTURALLY APPROPRIATE, EFFECTIVE STROKE PREVENTION PROGRAMS FOR NATIONWIDE IMPLEMENTATION IN MINORITY COMMUNITIES.

BACKGROUND

Disease Burden

Although stroke remains the third leading cause of mortality in the United States and the leading cause of adult disability, the burden of stroke is greater among minority racial/ethnic groups by virtue of its higher incidence and mortality in these populations. The incidence of ischemic and hemorrhagic stroke is disproportionately high in the African American population and occurs at younger ages; moreover, these disparities may be increasing. 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. Patterns of accessing the existing health care system for acute stroke also vary among racial/ethnic groups; for example, minorities are less likely to use the emergency medical system when experiencing a stroke. The reasons for these racial/ethnic variations in stroke-related risk factors and utilization of health care are not fully understood. Prevention programs are a preferred strategy for reducing or eliminating racial/ethnic disparities in stroke and include both primary and secondary approaches.

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.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH has established a program to create Nursing Partnership Centers to reduce health disparities. These centers will establish collaborations between research-intensive schools of nursing and minority-serving university schools of nursing to address health disparities, including stroke. The Centers will focus on influential factors that reduce health disparities, such as ways to promote healthy behaviors, reduce risks that contribute to chronic diseases, and develop ethnically and culturally sensitive health care interventions. Qualifying minority-serving institutions 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 encouragement of minority faculty, students, and investigators.

Building on several years of experience with an acute stroke research and care center in the Washington, D.C. metropolitan area, another hospital, which serves predominantly nonwhite, Hispanic,

and Latino populations, will be recruited to conduct a study of the epidemiology of stroke, barriers to acute stroke care, and the effectiveness of treatments and quality of care within the specific racial/ethnic communities served by the hospital. The study also will address how to tailor stroke prevention and intervention programs to those populations.

To develop sustainable, replicable, and culturally appropriate prevention and intervention research programs targeted to minority populations and designed to decrease the incidence and prevalence of stroke, NIH will establish a Stroke Prevention/Intervention Research Program (SPIRP) at a minority institution. The Program will identify more effective methods of implementing stroke prevention programs. Over a 2-year period, the first phase of the program will establish an infrastructure for the SPIRP. The second phase will establish collaborative stroke prevention research projects to include community-based interventions, epidemiology, and/or outcome measures. Ultimately, the SPIRP will identify effective, community-based stroke prevention and intervention strategies for export to and adaptation in other diverse communities.

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

PERFORMANCE MEASURES	BASELINE	FY 2004	FY 2005
Establish a 5-year program to create about 12 to 14 Partnership Centers to Reduce Health Disparities that will focus on influential factors that reduce health disparities.	(FY02) Piloted programs to build nursing center research capacity focused on health disparities		
FY 03	*Actual Performance:* (MET) Seventeen Nursing Partnership Centers established to reduce health disparities, including stroke, which link research-experienced nursing schools with minority-serving nursing schools across the nation.		
Establish a minority-focused, acute stroke research and care center to conduct a study of the epidemiology of stroke, barriers to acute stroke care, and quality of care within the specific racial/ethnic communities being served by the care center.	(FY03) Acute stroke center exists but is not focused on stroke disparities or in a minority community		
FY 04	*Actual Performance:* (MET) Acute stroke care center serving a minority community in the Washington DC metropolitan area has been established.		
Establish the infrastructure for a Stroke Prevention and Intervention Research Program (SPIRP) at a minority institution.	(FY03) Minority institution research/training programs exist but not on stroke prevention/intervention	o	
I	*Actual Performance:* Performance results will be reported in February 2006.		
Establish the infrastructure for a pilot Alaska Native Stroke registry that will facilitate identifying risk factors and strategies to improve stroke prevention and quality of stroke care provided to Alaska Natives.	(FY04) Several registries for Alaska Natives exist, including for cancer and diabetes, but none for stroke		o
FY 06	*Actual Performance:* Performance results will be reported in February 2007.		

O Target Active • Target Met — Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The target was met through establishing an acute stroke care center at the Washington Hospital Center (WHC), a private community hospital in Washington DC where more than 75 percent of stroke patients are either African American or Hispanic. Operations began at the center in October 2004, and a NIH Stroke Team is available through the WHC's Emergency Department 24 hours-a-day, 7 days-a-week to guide treatment of all stroke patients. The stroke center is recruiting patients for five active investigational treatment protocols and a program is in place to assure that all stroke patients at WHC receive proper medicines and risk factor education for secondary stroke prevention. In addition, the center is planning community outreach efforts which will be implemented in FY 2005. Construction of a cutting-edge 3 Tesla MRI facility is underway. The facility will enhance the ongoing study of stroke and heart disease in this population and is expected to be central to the investigation and development of new stroke therapies.

Implementation Strategy Advances or Other Highlights. Progress on reducing health disparities continues at the Nursing Partnership Centers (NPCs). Fifteen pilot studies have begun at the NPCs involving nearly 1000 minority subjects, as well as scores of minority investigators who are conducting the research and developing expertise in health disparities research. In addition, twelve universities paired with the NPCs are conducting educational activities to promote healthy behavior including stroke prevention among minority Americans.

In support of the FY 2005 target, NIH awarded a cooperative agreement grant to the Morehouse School of Medicine in Atlanta, Georgia, in June of 2003 to establish a SPIRP. The Program is the first clinically oriented intervention program to be allied with the SNRPs at minority institutions. The six-year award includes a two-year infrastructure development and planning phase which is currently underway.

In support of the FY 2006 target, the NIH has received an application from the Alaska Native Medical Center, which currently maintains Alaska Native registries for cancer and diabetes, for the establishment of a pilot Alaska Native Stroke Registry. The application is currently under review.

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

In September 2004, five research grants were funded in response to the RFA "Interventions to Improve Hypertension Control in African Americans." The program was established to evaluate clinically feasible interventions to increase treatment of hypertensive African Americans. The program will enroll near 3,900 patients in community-based health care settings to test various approaches to improving blood pressure control in African Americans. In addition, applications were received in response to the "Reducing Health Disparities through Risk Factor Self-Management" Program Announcement and are currently under review.

Communication and Transfer of Results

Without the flow of information, important scientific findings would languish at the researcher's bench. The benefits NIH's research activities cannot affect human health unless that knowledge is disseminated. Thus, a core NIH function is to facilitate the communication of research findings to clinicians, the public health system, voluntary health organizations, and the public. Equally important is transferring knowledge to the private sector so that it can be used to develop products

and technologies that benefit health. NIH's technology transfer program is one of the most active in the Federal Government.

The Public Health Service Act of 1944 authorized NIH and the other U.S. Public Health Service (PHS) agencies to collect and make available, through publications and other appropriate means, information relevant to the practical applications of research [Title III, Sec. 301 (1)]. In addition, the legislation that enables and directs the development of NIH programs emphasizes the important role NIH plays in informing the public about the results of health-related research. All of the NIH ICs conduct programs to collect, disseminate, and exchange information on medical and biological science, medicine, and health. The National Library of Medicine (NLM), the world's largest medical library, is a component of NIH and works closely with the ICs to ensure the effective communication of research results.

The broad purpose of NIH's technology transfer activities is to facilitate and enhance the development of new drugs, other products, and methods of treatment that benefit human health by promoting the efficient transfer of new technologies resulting from NIH research to the private sector. Federal legislation empowers NIH to interact directly with industry to expedite the transfer of technological discoveries into commercial products that will benefit the public. NIH patents technologies invented by its intramural scientists and issues licenses to organizations in the private sector that are willing and able to commercialize these inventions. NIH has forged numerous partnerships with industry and other external research organizations, thereby enhancing its capacity to expedite the commercial application of these new technologies with the ultimate goal of improving the public health and advancing the research enterprise.

Partnerships are as crucial to the communication and transfer of results as they are to generating new knowledge. Community-based and international partnerships are especially featured in the goals that follow, and these partnerships are important vehicles for gathering as well as for disseminating information.

The table summarizes the performance goals and due dates included in this section:

Communication and Transfer of Results	
CTR-1)	By 2008, reduce the disparity between African American and white infants in back sleeping by 50% to further reduce the risk of Sudden Infant Death Syndrome (SIDS).
CTR-2)	By 2006, increase awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least five communities and extending the impact of the NINDS Campaign, "Know Stroke: Know the Signs. Act in Time."
CTR-3)	Through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products. (Ongoing)
CTR-4)	Increase the percentage of SBIR award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization. (Ongoing)
CTR-5)	*By 2013, improve marketing and management of NIH intellectual property (IP) assets by building data mining capability.*

CTR-1) BY 2008, REDUCE THE DISPARITY BETWEEN AFRICAN AMERICAN AND WHITE INFANTS IN BACK SLEEPING BY 50% TO FURTHER REDUCE THE RISK OF SUDDEN INFANT DEATH SYNDROME (SIDS).

BACKGROUND

Sudden Infant Death Syndrome (SIDS) is a syndrome of unknown cause and is defined as the sudden death of an infant under one year of age, which remains unexplained even after a thorough case investigation, autopsy and review of the clinical history. SIDS is the leading cause of post neonatal mortality in the U.S. According the National Center for Health Statistics, the 2002 SIDS rate is 0.57/1,000 live births. The national *Back to Sleep* public health education campaign was launched in 1994 after the American Academy of Pediatrics (AAP) recommended back sleeping as the safest sleep position for infants under 1 year of age. Stomach sleeping is a major risk factor for SIDS. The campaign promotes placing babies on their backs to sleep to reduce the risk of SIDS. It is led by the NIH in collaboration with the following campaign sponsors: AAP, Maternal and Child Health Bureau of HRSA, First Candle/SIDS Alliance, and the Association of SIDS and Infant Mortality Programs.

Rationale

Since the launch of the campaign in 1994, the SIDS rate has dropped by 50 percent. However, despite the overall success of the campaign, African American infants are placed to sleep on their stomachs more often than white infants. The SIDS rate for African American infants is two times greater than that of white infants.

The NIH and other campaign sponsors hosted a meeting of experts to identify strategies for reaching African American communities with the *Back to Sleep* campaign messages. Representatives from various organizations including the Alpha Kappa Alpha Sorority, Inc. (AKA), Women in the National Association for the Advancement of Colored People (WIN), National Coalition of 100 Black Women (NCBW), National Medical Association, and the Congress of National Black Churches, Inc. and others proposed outreach and education strategies aimed at eliminating the racial disparity in SIDS rates. As a result, the NIH and partner organizations developed the *Resource Kit for Reducing the Risk of SIDS in African American Communities,* which is designed to help organizations initiate SIDS risk reduction programs in their local communities. It contains materials such as facts sheets and brochures to encourage people to lead discussion groups on ways to reduce the risk of SIDS in various community settings.

The *Partnerships for Reducing the Risk of SIDS in African American Communities* was a project with the AKA, NCBW, and WIN. The leaders of these three organizations committed to hosting three summits featuring the NIH SIDS risk reduction information and materials. The following is a list of the summit locations that were held in FY '03: 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.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Various strategies have been developed to satisfy the overall goal of SIDS reduction in African American communities. First, regional summits were held across the country to train and educate local community members and leaders about SIDS and to raise awareness about approaches to reducing

SIDS risk. Representatives of organizations attended to ensure that appropriate guidance was delivered. 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. Second, the NIH will conduct informal interviews to determine subsequent outreach strategies that developed as a result of their participation. Third, NIH will identify a minimum of six national organizations that can help promote the *Back to Sleep* campaign messages to local communities. Fourth, NIH will work with nursing organizations to promote *Back to Sleep* campaign messages to their members who have access to patients who may directly benefit from the information.

PERFORMANCE MEASURES	BASELINE		FY
In collaboration with African American organizations, community health and other local officials, and faith-based organizations, conduct regional summit meetings to train and motivate individuals who will implement SIDS risk reduction activities in their communities.	(FY02) No regional summit meetings were held prior to 2003		
Actual Performance: (MET) Over 1,000 participants were trained and motivated to reduce SIDS in African American communities during 3 regional U.S. summits.			
Conduct 250 interviews among the approximately 1,500 participants who attended the three summit meetings held in FY 2003 to determine that each summit resulted in a minimum of 50 outreach activities.	(FY03) No interviews have been conducted for this purpose		
Actual Performance: (MET) Interviews were held with participants from each summit and over 50 outreach activities resulted from each of the summits.			
Continue to extend "Back to Sleep" campaign messages to African American populations through community-based collaborations/partnerships by involving a minimum of six national organizations in SIDS training and educational activities.	(FY03) Three participating national organizations		o
Actual Performance: Performance results will be reported in February 2006.			
Promote a continuing education module with at least six national nursing organizations serving African American communities to extend the *Back to Sleep* campaign messages.	(FY03) There are no known efforts to systematically educate the nursing community on national level about SIDS risk reduction		o
Actual Performance: Performance results will be reported in February 2007.			

o	Target Active	•	Target Met		Target Extended	X	Target Not Met

Summary of FY04 Performance Results

Target. The FY 2004 target was met. Over 250 interviews were held (represented by approximately 550 reaction forms) with attendees from the three summits to explore the ways attendees intended to use the SIDS information when returning to their communities.

The target of 50 outreach activities as a result of each summit was exceeded. Activities ranged from mini-summits in various cities across the country, "SIDS Sundays" in churches in certain regions of the country, and mini-grants from the CJ Foundation for SIDS to African American organizations to conduct local outreach activities using NICHD SIDS risk reduction materials.

Approximately 6,500 *Resource Kits for Reducing the Risk of SIDS in African American Communities* have been distributed since the first summit was held in January 2003. In parallel, the NIH developed a brochure and other supporting materials for ease of distribution. After the summits were held, brochures

were distributed at levels approaching 75,000 units per month with two peak months of over 200,000 units being delivered to outreach outlets in the community.

Implementation Strategy Advances or Other Highlights. In conjunction with Alpha Kappa Alpha Sorority, Inc. (AKA), the National Coalition of 100 Black Women (NCBW), and the Women in the NAACP (WIN), the NICHD/NIH formed the *Partnerships for Reducing the Risk of SIDS in African American Communities* to achieve this target. The leaders of these three organizations made a commitment to sponsor three summits featuring the NIH SIDS risk reduction campaign information and materials. Leaders and members of the AKA, NCBW, and WIN, participated in all three regional summits. The purpose of the summit meetings was to encourage the health and community leaders in each region to engage in SIDS risk reduction activities, build alliances within communities to assist in SIDS risk reduction activities, educate those with the power to make a change in policy or behavior, and create collaborative models and resources that can remain within communities.

Using the NICHD's SIDS risk reduction materials, the AKA members developed a Mother's Day card project, culminating in the distribution of 200,000 of the NICHD's Mother's Day cards through a network of 45,000 active chapter members.

Efficiency. The number of planned outreach activities (50) was exceeded due to the high-level of community group involvement.

CTR-2) BY 2006, INCREASE AWARENESS AMONG THE GENERAL PUBLIC ABOUT THE SYMPTOMS OF STROKE AND THE NEED TO SEEK TREATMENT RAPIDLY BY PARTNERING WITH PROVIDERS AND VOLUNTEERS IN AT LEAST FIVE COMMUNITIES AND EXTENDING THE IMPACT OF THE CAMPAIGN, "KNOW STROKE. KNOW THE SIGNS. ACT IN TIME."

BACKGROUND

Stroke places a major health burden on U.S. society in death, disability, and economic costs. About 700,000 new strokes (first and recurrent) are reported every year in the United States. Stroke is the third leading cause of death and is a leading cause of serious, long-term disability among adults. Stroke costs the United States $51.2 billion per year in direct and indirect costs. To bring important health messages to the public and in response to the mandate by Congress in the FY 2001 House and Senate Appropriations Committee reports, the NIH created the multifaceted communication effort "Know Stroke. Know the Signs. Act in Time." The campaign aims to increase awareness of the symptoms of stroke and the need for urgent action. Next year, NINDS will focus its campaign resources in at least five communities where the impact of stroke is particularly great.

In addition, NINDS will begin an outreach program targeted specifically to African Americans because the need for stroke information is especially important among this population. African Americans suffer strokes at a disproportionate rate and are more likely to die from them than other racial groups.

Stroke is a medical emergency. Rapid identification of a stroke is essential to treatment and positive outcomes. When given within 3 hours of the onset of symptoms, a clot-busting drug called tissue-type plasminogen activator (t-PA) can reduce and even reverse the impact of a stroke by dissolving the blood clot that causes damage to the brain. An NINDS study found that patients who received t-PA were at least 30 percent more likely to recover with little or no disability after 3 months. Without t-PA, stroke patients often suffer disabilities that require extensive rehabilitation. The window of opportunity to

start treating stroke patients is 3 hours from the onset of symptoms, but to be evaluated, patients should arrive at the hospital within 60 minutes.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The "Know Stroke" campaign is a multiphase effort. In the first phase, NIH developed materials in collaboration with key stakeholders in the stroke community, and focused efforts on reaching health care providers. In the second phase, NIH developed and executed transit public service advertising in communities across the country where stroke has a particularly negative impact.

In FY 2004, NIH will continue to cultivate its partnership with ASA to extend the "Know Stroke" campaign. NIH is organizing a strategy session with ASA Operation Stroke program directors from 20 communities across the country. Using the "Know Stroke" materials and information, ASA program directors will work within their communities to educate providers and the public about the importance of rapid treatment for stroke. Five of these communities will receive special focus in FY 2004.

During FY 2004, 3,000 "Know Stroke" community education kits will be distributed within local communities with at least 15 percent African American population, and 100,000 "Know Stroke" brochures will be distributed (of which 25,000 will be distributed to African American audiences). In addition, NIH will initiate strategic activities to reach African Americans.

Using a phased approach, NIH will participate in and disseminate materials at large cultural events within the African American community in Washington, D.C. NIH will then seek to build partnerships through ASA and African American organizations in targeted areas with large African American populations to disseminate materials and messages and extend the reach of the "Know Stroke" campaign into communities most affected by stroke. During FY 2005, NIH will distribute an additional 5,000 kits (of which 1,000 will be through African American partners).

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2006	FY 2007
Work with partners in five communities with at least 15 percent African American audiences to extend the "Know Stroke" campaign messages by attending community fairs and collaborating with local leaders and health educators to disseminate 3,000 "Know Stroke" community education kits and 100,000 "Know Stroke" brochures (25,000 will be distributed to African American audiences).	(FY03) National partnerships developed; no current comprehensive local partnerships				
IFY 04	*Actual Performance:* (MET) Completed outreach programs in 5 U.S. cities. Distributed 109,619 brochures, including 27,236 to African American audiences. Distributed 3,000 kits through national marketing campaign to city and county health officials.				
Extend the outreach program to an additional five communities nationwide, arming community leader with tools and information to distribute an additional 5,000 "Know Stroke" community education kits (1,000 will be through African American partners).	(FY03) Five partnerships developed in FY 2004		o		
	Actual Performance: Performance results will be reported in February 2006.				
Work with national organizations such as the CDC, the National Council of La Raza, and the Urban League to develop community-based programs for extending the Know Stroke messages to Hispanics and African Americans in at least 10 markets.	Partnerships established through community based outreach in FY 2004			o	
	Actual Performance: Performance results will be reported in February 2007.				

|""O Target Active | • Target Met | — Target Extended | X Target Not Me7~|

Summary of FY04 Performance Results

Target. The FY2004 target was met. NIH conducted outreach programs in 5 U.S. cities and distributed 109,619 Know Stroke brochures through targeted educational programs, including 27,236 brochures to African American audience. Additionally, 3,000 Know Stroke community education kits were distributed through an ongoing national marketing campaign to city and county health officials.

Implementation Strategy Advances or Other Highlights. In cooperation with the partners and community organizations, NIH completed outreach activities in 5 cities across the U.S. with a 15% African American population, including Houston, Richmond, Chicago, Birmingham, and New Orleans.

NIH worked with the CDC to develop and produce outreach materials for the program, including an African American brochure that has been well received in the community. Working with the ASA, NSA, and CDC state heart disease and stroke prevention programs in each city, NIH identified 10-12 individuals who were active in the senior citizen, African American, and Hispanic communities. These people, NIH/CDC "Stroke Champions", were trained about stroke and how to discuss the *Know Stroke* campaign materials within their communities. They brought education about acute stroke to the local level by conducting outreach activities at community events in each city.

Following the outreach activities undertaken, three groups contacted the NIH with an interest in developing state-wide programs based on the *Know Stroke* messages and materials. Activities are currently being planned with the following working groups: Texas Department of Health (extension of Houston outreach), Illinois Rural Health Association (extension of Chicago outreach), and the Delta States Consortium (extension of Birmingham and New Orleans outreach).

Efficiency. The NIH exceeded its distribution target of 100,000 *Know Stroke* brochures by 9,619.

CTR- 3) THROUGH EDUCATION AND TECHNICAL ASSISTANCE, STRENGTHEN THE CAPACITY OF DEVELOPING COUNTRIES TO IDENTIFY TECHNOLOGIES AND PURSUE THEIR DEVELOPMENTINTOPRODUCTS. (ONGOING)

BACKGROUND

NIH has a longstanding tradition of promoting science with the ultimate goal of improving the public health on a global scale. One manner in which this is accomplished is by ensuring the availability of new therapeutic drugs, vaccines, devices, and other products that improve human health by linking technologies resulting from NIH and FDA intramural research with the private and public sectors through Public Health Sector (PHS) technology transfer activities. In this regard, NIH, on behalf of HHS, is one of the most active agencies in the Federal Government, participating in infrastructure and policy-building workshops hosted in the U.S. and overseas. OTT's participation in symposiums and workshops usually includes meetings and discussions with foreign delegations interested in replicating or adapting the successful partnerships among government, industry, and academia occurring within the United States.

To more fully utilize these partnerships to meet the NIH mission, there is a need to enhance the capacity of key personnel in developing countries to adapt and build the infrastructure for transferring laboratory discoveries to the bedside. Capacity building, within countries, is best achieved with active participation by local experts. Sometimes, however, local expertise first must be developed. This can

be achieved by establishing a program for providing technical assistance and specific information to scientific and administrative personnel in developing countries on technology transfer activities and operations. This program can be carried out first with countries identified through previous collaborations as having the foundation (e.g., R&D experience, cadre of scientists, and government interest in science, technology and commercialization) necessary to establish technology transfer offices.

Rationale

The mission of the NIH, an Agency of the Department of Health and Human Services (HHS), is to support "science 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." Thus, promotion of science at NIH has the goal of not only improving the health of the American public but also ultimately enhancing human health on a global scale.

The OTT supports this goal by ensuring through its technology transfer activities that PHS health-technologies become available to the public in the U.S. an abroad. Moreover NIH institutes and centers are increasing their efforts worldwide by supporting centers of excellence in developing countries. The proposed international capacity building program will join in the NIH effort to be sure that countries receiving NIH funds have the ability to appropriately handle patents and licenses arising from NIH funding. It is a requirement that NIH grantees comply with Bayh-Dole provisions and thus need training on handling such matters appropriately consistent with the terms of their grants, the law, and U.S. policy interest. This is also in the U.S. public interest and, ultimately, results in improvement in public health.

As noted in the NIH Roadmap, "public-private partnerships have become a model for advancing science and communicating results of medical advances to improve the quality of life for all people." In its routine functions relating to intellectual property, patents and licensing, and through its daily interactions with NIH scientists, universities and industries, OTT has been at the forefront of this endeavor. Thus, undoubtedly, OTT can provide leadership through this technical assistance program in building bridges worldwide "among researchers in academia, government and the private sector" to move research results and to make technologies accessible to the public in form of products.

HHS is committed to "finding and sharing solutions to shared health problems with our global partners". This goal of strengthening the capacity of developing countries to identify technologies and pursuing their development into products fits within the spirit of the HHS Office of Global Health Affairs, which is charged with the mission of "promoting the health of the world's population by advancing the Department of Health and Human Services' global strategies and partnerships" including those global efforts targeted to reduce the burden of diseases such as HIV/AIDS, tuberculosis, and malaria.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Establishing an in depth and long-term technology transfer assistance (TA) program to provide guidance and information related to technology transfer to scientific and administrative personnel in the appropriate institutions within developing countries will require extensive preparation. NIH plans to establish a working group in the Office of Technology Transfer (OTT) that will formulate recommendations. The recommendations will serve as the basis for a proposal for a needs assessment study that can be supported through the NIH One Percent Evaluation Set-Aside Program. This formal need assessment will systematically detail the nature and extent of issues that the technical assistance program should address and determine appropriate program goals and outcomes.

The strategy for program design (including selection of training personnel) is dependent on the outcome of the needs assessment, but NIH expects to initiate that process in FY 2005. NIH will identify appropriate institutions in developing countries that are in need of targeted technical assistance to address national and regional public health needs, and will administer appropriate capacity-building activities.

Securing potential partners is critical for full implementation of the technical assistance program. Thus, during FY06, potential partners from international organizations, private foundations, other federal agencies and professional societies will be identified. Identifying and acquiring these partners will require intensive dialogue and negotiations with numerous organizations and agencies, and relating the aim of the technical assistance program to their respective objectives, goals, missions, and strategic plans. Additionally, must commit to providing guidance and support throughout the development and implementation of the technical assistance program. As partners sign on to the goal, the program is likely to sustain itself and expand.

PERFORMANCE MEASURES	BASELINE		FY 2004		
Develop a needs assessment study for a technical assistance program in technology transfer for developing countries to systematically detail the nature and extent of issues that the TA program should address.	(FY03) No known needs assessment studies exist for developing technology TA program		-	-	
Actual Performance: (EXT) Funding was not approved, although international partners and personnel were secured to initiate the TA program.					
Based on results of the needs assessment, recruit and select personnel to design and implement the technical assistance program.	(FY03) No personnel			o	
Actual Performance: Performance results will be reported in February 2006					
Identify and target appropriate institutions in at least three developing countries in order to educate members on adapting and building infrastructure for transferring laboratory discoveries to the bedside.	(FY03) Limited access to targeted training in developing countries			o	
Actual Performance: Performance results will be reported in February 2006					
Secure potential supporting partner(s) to support the onset of the technical assistance program.	(FY04) While no organizations have been formally approached to serve as partners in supporting the technical assistance program. This follows informal discussions concerning the synergies and potential advantages of working with different organizations while participating in domestic and foreign meetings.				o
Actual Performance: Performance results will be reported in February 2007					

O Target Active • Target Met -> Target Extended X Target Not Met

SUMMARY OF **FY04** PERFORMANCE RESULTS

Target. The FY2004 target was extended. A proposal for One Percent Set-Aside funds was developed to support a needs assessment study that would enable the Office of Technology Transfer (OTT) to systematically detail the nature and extent of issues that the Technical Assistance program should address. Funds were sought from the NIH Office of Evaluations to conduct a needs assessment to assist OTT in the program design, but were denied.

After the initial proposal was denied, it was revised and resubmitted. Although neither proposal for Set-Aside funds was approved during the FY04 cycle, other potential sources of financing were sought. OTT is committed to this GPRA goal, but the extent to which it can be accomplished depends on securing funds.

In FY 2004, an intern from the United Kingdom and an American Association for the Advancement of Science (AAAS) Fellow were recruited to work specifically on issues pertaining to technology transfer in lesser-developed countries. Additionally, OTT staff participated in a workshop with reference to enhancing negotiating skills with private organizations, regional & international organizations and Public Private Partnerships.

Recent trips by OTT staff to Argentina, Chile, India, China, and Mexico were targeted to enhance OTT technology transfer activities with institutions in developing countries as well as technical assistance. OTT plans to expend time working on the various aspects of the Technical Assistance program, beyond the original brief, during a trip to Brazil scheduled for FY2005.

Implementation Strategy Advances or Other Highlights.

OTT secured partners from three international organizations to sponsor the training of interns from China, Ireland and India about technology transfer activities and operations in FY05. Negotiations are in progress, with two agencies, to extend training to Brazilian and Mexican scientific and administrative personnel.

Two articles that provide guidance as to how to carry out technology transfer in developing countries were accepted for publication in *IP Strategy Today* and the *International Journal of Microbiology*.

OTT developed a database of institutions with R&D potential worldwide. OTT has provided this database to the Centre for the Management of IP in Health R&D (MIHR) so they can enhance their technical assistance activities in Africa. This collaboration extends to the development of training workshops (upon the availability of funds) in the fields of intellectual property management of health research; in different African and Latin American countries. OTT is working with MIHR and other stakeholders on the opportunity to develop a database of relevant technologies to institutions in developing countries

OTT's strategy also includes participating in panel discussions of professional organizations and organizing a workshop. Specifically, two OTT staff will participate in panels at the Association of University Managers (AUTM) & the Gordon Research Conference in 2005; both related to technology transfer & technical assistance in developing countries. Furthermore, OTT has planned to coordinate a workshop in March 2005 with several universities in the Mid-Atlantic region; aimed at enhancing technology transfer activities in developing countries.

OTT is part of a Trans-NIH planning committee that is developing an implementation plan for three technical assistance workshops including topics related to grants management, intellectual property rights, technology transfer, and related activities in countries from Eastern Europe, Russia, and the Caribbean. OTT is also part of a working group coordinated by AAAS that includes representatives from Industry, Government, and University focusing on intellectual property management issues that could enhance the transfer and availability of health and agricultural technologies to institutions in developing countries. One of the expected outcomes is to publish a report that will include several examples pertaining to NIH technology transfer activities in lesser-developed countries.

CTR-4 INCREASE THE PERCENTAGE OF SMALL BUSINESS INNOVATION RESEARCH (SBIR) PROGRAM AWARD RECIPIENTS WHO ARE SUCCESSFUL IN IDENTIFYING THE RESOURCES

AND/OR PARTNERS NECESSARY TO FURTHER THE DEVELOPMENT OF THEIR SBIR PROJECTS TOWARD COMMERCIALIZATION. (ONGOING)

BACKGROUND

Established under the Small Business Innovation Development Act of 1982 (Public Law 97-219), the Small Business Innovation Research (SBIR) program was initiated to stimulate technological innovation, use domestic small businesses to meet Federal research/research and development (R/R&D) needs, foster and encourage participation by socially and economically disadvantaged persons and women-owned small businesses in technological innovation, and increase private sector commercialization of innovations derived from Federal R/R&D.

The SBIR program is a highly competitive, three-phase award system. In Phase I, the objective is to establish the technical merit and feasibility of the proposed R/R&D efforts and determine the quality of performance of the small business awardee organization prior to providing Federal support. In Phase II, the objective is to continue the R/R&D efforts. In Phase III, the objective is for the small business to pursue, with non-SBIR funds, the commercialization objectives resulting from the research conducted in Phases I and II. Early-stage financing of innovation through public-private sector partnerships, such as those in the SBIR program, plays an instrumental role in supporting the development of new technologies and is an effective means for accelerating the progress of the technology from the laboratory to the market. The small business research community often lacks the expertise, contacts, and funds necessary to support the commercialization of products/processes/services that are developed with NIH SBIR funds.

Rationale

To facilitate the translation of SBIR innovations into commercially viable products that will have societal benefit, NIH will develop a program of technical assistance services. These services will assist SBIR awardees in their transition from the "test tube to the medicine cabinet" and will serve as a means for leveraging NIH resources (SBIR funds) to foster new public-private sector partnerships. Because areas of need are varied and numerous, NIH envisions providing a "menu" of services from which SBIR awardees can choose to address their individual needs. Through the development of technical assistance programs, NIH will be able to catalyze the matching of SBIR recipients with the resources/partners needed for them to bring their concepts to commercialization.

By consolidating the funds available through individual awards, NIH can create a program to assist SBIR awardees as they address the technical challenges that arise during the conduct of SBIR projects. NIH has already conducted a pilot technical assistance program and plans to solicit proposals for contracts to provide other services/programs focused on technical and commercialization issues. The recently completed pilot was for a Commercialization Assistance Program (CAP). This program offered Phase II awardees business planning assistance and opportunities to "marry" their technologies with potential targeted strategic alliances and investors.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Several technical assistance programs aimed toward commercializing SBIR-developed products will be developed over a three-year period to meet the SBIR GPRA goal. The intent is to develop a menu of assistance programs from which SBIR awardees may choose to enroll that will help them fill a void in their ability to commercialize their federally-funded technologies. To achieve this end, modules expected to assist in the commercialization of SBIR products will be piloted. Effective pilots will be transitioned into programs. At that time, critical elements for monitoring performance will be identified.

These critical elements will be monitored over time to report on performance and to make adjustments as needed to enhance the services.

NIH will first pilot programs that expand the availability of business planning and strategizing assistance to small businesses. These pilots will target specific commercialization issues such as business planning, technology valuations and niche assessments, manufacturing issues, regulatory hurdles (for biologics, therapeutics, new drugs, and devices) and licensing. Programs that are successful in their pilot phases will be introduced to the greater pool of SBIR awardees the following year. For example, NIH will use the results of the recently completed (FY 03) Pilot Commercialization Assistance Program (CAP) to develop a trans-NIH CAP Program in FY 04. The program will include one-on-one business counseling; development of a business/ strategic plan; and identification of key customers, investors, and business partners. Fifty SBIR awardees participated in the business planning portion of the pilot. Of these participants, 35 presented their business opportunities at an investment event with the intention of attracting and/or obtaining investment funding and/or strategic alliances. These companies will be tracked for a period of 18 months to determine if they did in fact make an investment or partnering deal.

While the trans-NIH CAP program is being implemented, a minimum of one new pilot technical assistance program will be launched in another business area of need. A pilot Technology Assessment and Valuation Services Program (TAVSP) will be offered to a group of Phase I SBIR awardees. This program is intended to assist the companies with identifying the niche markets that may be applicable for the individual technologies being developed. From the lessons learned from the pilot, a trans-NIH TAVSP program will then be implemented in FY 05 provided the pilot proves to have addressed the needs of the participants. Using the approach of pilot testing programs one year and implementing trans-NIH programs the next, by the end of FY 05, it is anticipated that a minimum of two programs will then be items on the Technical Assistance Program menu and that this trend will continue into FY 06. If each is successful in becoming a menu item, the final menu could consist of CAP, TAVSP, a Manufacturing Assistance Program, and an FDA Regulatory program. Implementation of these programs will be done through solicited contracts with business consulting firms specifically trained to provide such services.

PERFORMANCE MEASURES	BASELINE	FY 2004				
Pilot test specific technical assistance program(s) for further development of SBIR projects toward commercialization (FY 04) CAP (FY 05) Niche Assessment (FY 06) Manufacturing or FDA Regulatory Assistance	No current programs		•	o	o	
Actual Performance: (MET) Completed Pilot CAP with 50 participants. Selected vendor for pilot Niche Assessment Program.						
Actual Performance: Performance results will be reported in February 2006						
Actual Performance: Performance results will be reported in February 2007						
Implement effective piloted programs to create a menu of technical assistance programs	Pilot Assistance Programs (i.e., CAP, Niche, etc.)			o	o	
Actual Performance: (MET) Initiated trans-NIH CAP with 130 participants.						
Actual Performance: Performance results will be reported in February 2006						
Actual Performance: Performance results will be reported in February 2007						

PERFORMANCE MEASURES	BASELINE	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Report critical elements to assess advances of each technical assistance program	Pilot programs converted to program implementation		•	o	o	
04	*Actual Performance:* (MET) Pilot CAP-- 50 participants of which 35 presented business opportunity at investment event. At 6 month mark, 33% had increased sales or were in negotiation.					
	Actual Performance: Performance results will be reported in February 2006.					
	Actual Performance: Performance results will be reported in February 2008.					

O Target Active • Target Met Target Extended X Target Not Met

SUMMARY OF **FY04** PERFORMANCE RESULTS

Target. The target in FY2004 for implementing a trans-NIH Commercialization Assistance Program was met. An assistance program was developed and implemented to support SBIR Phase II awardees.

The FY 2004 target for implementing a pilot Niche Assessment Program has also been met. A vendor has been selected, project plans developed, and work began on exposing a group of companies to the opportunity to participate.

Implementation Strategy Advances or Other Highlights. Commercialization Assistance Program - A GSA Request for Quotations (RFQ) to implement the CAP for approximately 125 participants was released in May 2004. The Larta Institute in Los Angeles, California, was selected as the vendor to implement the program; whose work involved the identification of a pool of participants, establishing relationships with professional service organizations, identifying pools of potential strategic alliances and potential investors and preparing invitational materials.

Pilot Niche Assessment Program - A purchase order was put in place, via RFQ, with GSA vendor *Foresight Science and Technology* to perform 'Technology Niche Analyses' (TNA's) for 100 NIH SBIR Phase I awardees. A pool of participants was identified and invitations to enroll were distributed.

Efficiency. Commercialization Assistance Program - The final cost of the CAP program roll-out for FY 2004 was below budget. The implementation strategy resulted in a budget saving of $650,000.

Capacity Building and Research Resources

Developing a research infrastructure is essential for continual scientific observation, discovery, and advancement. The NIH infrastructure encompasses the appropriate combination of trained scientific investigators, technologies, and research facilities. The productivity of the research enterprise depends in large measure on the strength of the talent pool and on technological and other research resources available for use in investigations. Collectively, NIH seeks to (1) recruit and train qualified investigators, (2) implement data automation and streamlined business processing where possible, and (3) expand the availability of resources by implementing Web-based tools, grant applications, and administrative portals.

Training and Career Development

NIH's training activities are designed to increase the Nation's ability to attract and retain the best and brightest minds and develop a cadre of well-trained, highly skilled investigators who are ready to generate the scientific discoveries of the future. To nurture the talent base of investigators, NIH provides research training support at the pre-doctoral and postdoctoral levels, primarily through the National Research Service

Award (NRSA) Program and career development support. The NRSA is authorized under Public Law 93¬ 348, Section 487, of the Public Health Service Act. (Note: Effective with the enactment of Public Law 107-206 on August 2, 2002, the NRSA Program was renamed the Ruth L. Kirschstein National Research Service Award Program as a tribute to the exceptional contributions Dr. Kirschstein has made to NIH and the Nation.)

RESEARCH RESOURCES

The availability and accessibility of essential research tools, cutting-edge technologies, adequate facilities, animal models, reagents, and other repositories are fundamental to the productivity of the research enterprise. This is because research resources often set the boundaries as to which questions can and cannot be investigated. Within research resources, new information technologies (IT) to share, transfer, and mine vast amounts of complex data electronically are revolutionizing the conduct of science and the management, administration, and support of the research enterprise.

NIH has an active history of using IT to contribute to the success of its mission as well as to the efficiencies of all aspects of its administrative and scientific functions. For example, in February 2000 NIH launched ClinicalTrials.gov, a Web-based database that provides patients, family members, health care professionals, and members of the public with easy access to information on government- and industry-sponsored clinical trials. NIH also developed an IntraMall, a Web-based system for easily locating, ordering, and recording purchases of scientific supplies, computer equipment, and office supplies. IntraMall is the Federal Government's largest online purchasing system.

The promise of IT continues to be realized. Currently, NIH is involved in three major IT initiatives, known collectively as enterprise systems. They are the NIH Business System (NBS), the Clinical Research Information System (CRIS), and electronic research administration (eRA). In addition to contributing to the NIH mission, each of these systems, in its own way, supports the President's Management Agenda (PMA) and the Secretary's One HHS initiative. For example, the eRA is playing a major role in supporting the DHHS E-Grants initiative. E-Grants are intended to put a single, simple face on the currently complex tasks of finding Federal grant opportunities and applying for Federal grants. Moreover, the eRA will create a unified electronic mechanism for grant application and administration to eliminate the redundant, paper-based processes currently required.

Expanding electronic government (e-gov) is one of the five key elements of the PMA and was initiated to make better use of IT investments to increase efficiency, reduce the paperwork burden, and improve government response time. The Secretary has embraced the PMA by moving to implement a "One Department" philosophy across DHHS, that is, a vision to help DHHS evolve from a collection of distinct and separate agencies into "One Department." To achieve his goal of managing DHHS IT on an enterprise basis, the Secretary directed the development and execution of the Draft *DHHS Enterprise Information Technology Strategic Plan, FY 2003-2008* (March 2003). The Plan outlines strategic goals and strategic objectives that will advance the best and most effective DHHS IT resources and will drive progress for public health and human services. All the NIH enterprise systems dovetail with the draft DHHS Enterprise IT Strategic Plan.

The table summarizes the performance goals and due dates included in this section:

Capacity Building and Research Resource	
CBRR-1)	Recruit, train, and retain a diverse population of highly trained scientists in biomedical, behavioral, and clinical research using research training grants, fellowships, career development awards, and student loan repayment programs. (Ongoing)
CBRR-2)	Promote data sharing and provide information in real time by implementing and monitoring the NIH Business System. (By FY2010, the NBRSS will be in an ongoing status)
CBRR-3)	Streamline business processes and automate data movement by implementing, monitoring and updating the Clinical Research Information system (CRIS). (Ongoing)
CBRR-4)	Provide greater functionality and more streamlined processes in grants administration by developing and monitoring the NIH electronic research administration (eRA). (Ongoing)

CBRR-1 RECRUIT, TRAIN, AND RETAIN A DIVERSE POPULATION OF HIGHLY TRAINED SCIENTISTS IN BIOMEDICAL, BEHAVIORAL, AND CLINICAL RESEARCH USING RESEARCH TRAINING GRANTS, FELLOWSHIPS, CAREER DEVELOPMENT AWARDS, AND STUDENT LOAN REPAYMENT PROGRAMS. (ONGOING)

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 training program is to maintain a population of scientists that is well educated, highly trained, and dedicated to meeting the Nation's future health-related research needs. At the same time, NIH believes strongly that training and supporting a research community that reflects the Nation's diversity is a top priority. Accordingly, NIH has designed a number of training programs to provide support to a diverse population of graduate and postdoctoral students and to recruit them into research at all career levels. NIH also has developed programs designed to enhance the retention of women in biomedical research careers and support for individuals with disabilities. Continual monitoring of the demographics of the participants in NIH programs is an important aspect of fostering a diverse cadre of researchers able to conduct basic and applied scientific research.

This monitoring enables NIH to implement corrective actions. For instance, if application rates for a particular program fall below historical rates, NIH determines the reason and responds accordingly. Possible actions to enhance the attractiveness of a particular award include increasing applicants' probability of success (the success rate), increasing benefits for awardees, or improving outreach. Success rates affect the attractiveness of an award since applicants who think they are unlikely to receive an award may opt for other sources of support. It is, therefore, important for NIH to maintain stability in the overall success rate so that applicants know what to expect.

Success of NIH training programs can be measured by the number of trainees that apply for and receive subsequent NIH support; successful subsequent support is an indicator of retention in the research arena.

Rationale

The NIH is dedicated to improving the health of Americans by supporting biomedical research that will help prevent, detect, treat and reduce the burdens of disease and disability. In order to achieve these goals, it is essential to ensure a diverse available pool of highly trained scientists in adequate numbers and in appropriate research areas to address the nation's biomedical, behavioral and clinical research needs.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

During the implementation of this goal, NIH staff will assess the quality and relevance of existing programs by closely monitoring: (1) applications for pre- and post-doctoral trainees and fellows to ensure that awardees exceed comparison groups; (2) Training grants to ensure that the targeted 10% receive multidisciplinary/interdisciplinary training grants; and (3) the number of K23, and K24 and K30

awards. Additionally, NIH will increase the diversity of trainees by enhancing training and career development opportunities for individuals from disadvantaged or underrepresented groups. Finally, NIH will increase its pool of investigators by using student loan repayment programs. Rolling cohorts of students will be continually drawn from data sources to ensure ample data for comparison groups.

PERFORMANCE MEASURES *Note: Annual targets are grouped by*	BASELINE		FY 2004	FY 2005	FY	FY
Assess the quality and the relevance of existing research training and career development programs:						
Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation.	Award rates NRSA Group: 46% Comparison Group A: 35% Comparison Group B: 26%		•	o	o	
Actual Performance: (MET) Award rate to comparison groups exceeded by 12%						
Actual Performance: Performance results will be reported in February 2006						
Actual Performance: Performance results will be reported in February 2007						
Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support research grants exceeds relevant comparison groups by 10% within 10 years of termination[1].	(FY03) Applied for but did not receive = 174 recipients; 929 trainees Received last year of training support 10 years before = 324 recipients; 808 trainees.		•	o	o	
Actual Performance: (MET) Award rate to comparison groups exceeded by 14%						
Actual Performance: Performance results will be reported in February 2006						
Actual Performance: Performance results will be reported in February 2007						
Ensure that there is multidisciplinary /interdisciplinary training on at least 10% of all training grants as evidenced by program or trainees reporting different Field of Training, or Discipline/Specialty Field codes or departments	(FY03) 486 multidisciplinary grants - 46%		•	o	o	
Actual Performance: (MET) The reported rate of multidisciplinary grants was 44%						
Actual Performance: Performance results will be reported in February 2006						
Actual Performance: Performance results will be reported in February 2007						
Achieve 100% of the asymptotic targets for the number of K23, and K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research. 120 K23 FY04-FY06 50 K24 FY04-FY06 50 K30* FY04-FY06	(FY99-FY02) Awards granted K23 645 K24 263 K30 59		•	o	o	
Actual Performance: (MET) All annual targets achieved (K23 =222, K24 =50, K30 =59)						
Actual Performance: Performance results will be reported in February 2006						
Actual Performance: Performance results will be reported in February 2007						
Increase the racial and ethnic diversity of the pool of trainees:						

PERFORMANCE MEASURES *Note: Annual targets are grouped by*	BASELINE		FY 2004		FY 2005	FY 2006 / FY 2008
Increase by 1% over baseline the number of research training and career development positions occupied and enhanced opportunities provided to individuals from underrepresented racial and ethnic groups.	(FY03) Asian: 2,415 African American = 1,466 American Indian = 135 Pacific Islander[1] =72 Hispanic[2]= 975			o	o	
	Actual Performance: (EXT) Comparable statistics run every May; hence, annually reported measures to be re-configured to complete reporting in December of the reporting year.					
	Actual Performance: Performance results will be reported in February 2006					
	Actual Performance: Performance results will be reported in February 2007					
Increase the cadre of highly qualified investigators with the diversity and expertise to build capacity to conduct biomedical/behavioral research:						
Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	(FY03) Applications received = 1,881 Contracts awarded = 1,193			o	o	
	Actual Performance: (MET) Applicants 2,498, Awards 1,407 (56% of applicants received an award)					
	Actual Performance: Performance results will be reported in February 2006					
	Actual Performance: Performance results will be reported in February 2007					

O Target Active • Target Met Target Extended ° Target Not Met

Summary of FY04 Performance Results

Target 1. The target in FY2004 was met. Using comparable data from the span 1986 through 1993 (to correspond to the interval chosen by Pion)

	PERCENT SUBMITTING APPLICATIONS	PERCENT RECEIVING AWARDS
NRSA Study Group	33.1	20.5
Group A	13.8	7.0
Group B	6.5	2.9

Both the NRSA Study Group's Percentage Applying and Percent Receiving Awards exceed the comparable groups by greater than 10 percent.

Target 2. The target in FY2004 was met. Based upon data maintained by the NIH, the application and award rates for NRSA recipients substantially exceeded those of their comparison group. Of the 10,380 individuals who terminated NIH NRSA-Kirschstein postdoctoral fellowship support over the period from 1983 to 1993, 5,411 (52.1%) applied for research project grant support and of those, 3,602 received a grant (34.7% of the applicants).

Of the 10,560 unsuccessful applicants for NRSA NRSA-Kirschstein postdoctoral fellowship support, 3,784 (35.8%) applied for research project grant support and 2,199 of those received a grant (20.8% of those who applied).

Group	Applied for a grant	Received grant
NRSA	52.1%	34.7%
Other	35.8%	20.8%
Delta		**13.9%**

Target 3. The target in FY2004 was met. The NIH collects information on the Field of Training (FOT) at the time of each trainee's appointment and the NIH can track these opportunities to particular training grants. The research training grants, that include training positions, reporting more than one FOT are considered interdisciplinary for this target. As indicated in the baseline year (2003) the NIH found 486 institutional training grants that were considered multidisciplinary using this criterion. In FY 2004, the number had increased to 556 training grants or approximately 44% of all training grants reported.

Target 4. The target in FY2004 met all three key deliverables.

- In FY 2004, the NIH made 222 K23 awards and exceeded its target of 120, by 85%, in supporting the mentored, patient-oriented, career development experiences of young clinicians. This program has proven to be more attractive than originally anticipated as shown by the successful recruitment of additional individuals into patient-oriented career development experiences.

- In FY 2004, the NIH made 50 K24 awards and met its projected target for this program (50). The K24 program was developed to support mid-career, patient-oriented investigators who would be willing to devote 25 to 50% of their effort conducting research or serving as the mentor for an aspiring patient-oriented researcher like those supported by the K23s.

- In FY 2004, the NIH made 59 K30 awards and exceeded its target of 50. The Curriculum Development Award in Clinical Research (K30) is felt to be a highly effective program, funds have been identified to make further awards (50) in order to extend this program for an additional five year competitive cycle beginning in FY 2005.

Target 5. The target in FY2004 will be extended. The project period for many NIH Institutional Research Training grants is from June 1 through June 30 of the following year, during which time trainee appointments are made. Information regarding these appointments is relayed to the NIH throughout this time period; however, the majority of information is available after June 30. The percentage of under-represented minorities rose from 15.5% in FY 2003 to 16.2% in FY 2004. Because FY 2004 data is drawn in December 2004, values for some FY 2004 trainees have not yet been submitted to the NIH.

Consequently, the target is extended to align data mining with annual performance reporting requirements. To correct performance reporting in out years the data will be based upon the collection of two runs from the data. For example, the FY05 annual performance will be the construct of (Dec 04 - May 05) + (May 05- Dec 05) data. Each subsequent year will do the same to provide a consistent output of information.

Target 6. The target in FY2004 was met. The NIH received a total of 2,498 new and renewal applications for the 5 Extramural Loan Repayment programs in FY 2004. The NIH made 1,407 new and renewal awards; therefore 56% of applicants were awarded SLR contracts.

Explanation of Differences from Previous Submissions

Targets

Termination (in target 1) was changed to graduation to more accurately reflect what is being measured in the target/comparison group. Discipline/Specialty Fields and departments were addedjo

target 3 because program codes have evolved. The new specification allows for more complete and consistent comparisons of information between the past and the future. The baseline information for target 5 was updated based on additional data that has been filed. Changes were made to baselines for targets, as they did not adequately support the measurement of performance.

Target 1. The performance against this target is measured by the rate of which awards are granted to pre-doctoral trainees. The exiting baseline entry showed numbers of trainees only with no reference to the award rates observed; for which assessing the target of a 10% gap between NRSA and other comparison groups is key.

Target 4. Baseline information presented was replaced. This did not present a change to the baseline but a correction - prior entry had annual targets in the baseline section.

Target 6. The baseline was changed to show the award rate experienced in FY03. The target requires an increase in the numbers investigators retained through loan repayment programs. This update allows the reader to assess the reference point given the information found in the *About Performance* section.

CBRR-2) PROMOTE DATA SHARING AND PROVIDE INFORMATION IN REAL TIME BY IMPLEMENTING AND MONITORING THE NIH BUSINESS SYSTEM. (BY FY 2010, THE NBS WILL BE IN AN ONGOING STATUS.)

BACKGROUND

The core mission of the 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 most basic assumption is that 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 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.

As the system matures and the NBS General Ledger and Travel modules are in an operation and maintenance mode, the NBS will continue to identify baseline performance measures to achieve the "Improve Financial Performance PMA" goal. The systems goals are to enhance the overall federal financial management position by improving and integrating financial systems, improving decision support capabilities, improving the analysis of financial activity, maintaining unqualified opinions, and integrating financial management and performance data. Using FY 2004 baseline performance data, the NBS will assess the financial management and systems environments, review them in relationship to Federal, DHHS and NIH Enterprise Architectures and collect critical performance indicators. Analysis of these indicators should provide direction for improvements to the system, serve as a baseline to develop corrective strategies and, determine the necessity of system component upgrades. These are iterative activities; as each NBS module is deployed QC processes will assess critical performance functionality, develop corrective strategies when necessary and identify enhancements.

Rationale

The implementation of the NBS will create an integrated transaction processing system that promotes data sharing and provides information in real time, ultimately providing more integrated, thus efficient and cost-effective, administrative support to achieve NIH's scientific mission. Beyond sheer automation, this project seeks to combine the latest technology with proven best business practices and to provide a new level of support to research.

Implementation of the NBS is one of several administrative improvements that demonstrate the NIH's commitment to the principles behind the PMA, including improved financial performance and expanded electronic government. Specifically, it will (1) allow for greater integration of administrative processes with the financial system, and (2) encompass new financial systems to comply with all applicable accounting requirements and standards.

The NIH is required, by the Chief Financial Officers (CFOs) Act and the Government Management Reform Act (GMRA), to prepare annual financial statements covering all of its activities and to have the statements audited by independent auditors. The preparation of financial statements requires an integrated financial management system and processes that provide complete and accurate accounting data on a timely basis. Timeliness for the preparation and submission of audited financial statements has been redefined by OMB from 6 months following the end of the fiscal year in FY 1996 to 6 weeks in FY 2004. Timeframes for other required financial reporting have also been shortened.

Deployment of the NBS should position the NIH to meet the CFO Act and GMRA requirements and OMB's timeframes. Successful implementation of the NBS general ledger module for FY 2004 reduces the need for previously constructed adjustments required to prepare financial statements. This is 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 an important component of the One HHS initiative and a major element of the DHHS Unified Financial Management System (UFMS). As both systems mature, the NBS will merge into the single financial management system envisioned by DHHS. The NIH staff actively participates on DHHS UFMS teams to meet common goals, address Department-wide challenges, and ensure that the NBS will become an integral part of the UFMS.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The NBS Implementation is a phased approach, as recommended by JFMIP, to incorporate individual modules as they are completed. Modules of the NBS will serve similar functions to the legacy ADB system. The NBS is an integrated financial and administrative system. This integration is the most defining characteristic of the project. During FY 2003, the following modules were deployed: the general ledger/budgeting module and the travel module. In FY 2006, the NBS plans to deploy the contracts/ acquisition, property, supply, accounts payable and receivables modules and the agreement and real property solutions. Billing and cost accounting for Central Service and Supply operations will be deployed at a later date. Integration testing of the modules will ensure functional compatibility as appropriate. Additional modules may be developed and implemented beyond the original seven functional areas of ADB.

The current vision for the NBS system includes operational and strategic modules in the following categories/ areas:

GL and Federal Administration	Purchasing
AP	Research and Development Contracts
AR	Supply/Inventory Management
• Project Accounting	[Accountable] Property Management

The generic IT development plan applies to all modules being developed to support the NBS. Whilst, parallel activities occur there are many 'gateway' dependencies and as such timing delays, or re-runs of activities occur. Globally, the key challenge once the assembled modules are linked is to ensure sufficient IT architecture and 'coding' as to provide efficient intra-module communications and linkages

The FY 2005 and FY 2006 NBS implementation and deployment activities that the functional, technical and change management teams will undertake include the ongoing design, configuration, and testing of the baseline system and the system at the integration phase including workflow management.

An overview of the tasks follows:

a) identifying business rules to be applied and functionality that have policy change implications;
b) testing each function to assure that the configurations are accurate, that business rules are being applied properly and reporting test results for potential change management issues;
c) developing workflows for each function and identifying all interfaces with other functions;
d) testing integrated functionality to determine that business rules and workflow operate as expected and report the results
e) defining all existing integration with remaining ADB function(s) or other systems, as required;
f) developing acceptance test criteria and translating the acceptance test criteria into test scripts for the end user training and for the functions to be deployed;
g) collaborating with Change Management staff to develop technical training materials and user documentation for each function to be deployed;
h) training approximately 6200 users for an estimated 32 roles and
i) providing access to all authorized NIH users of each new function and providing pre and post deployment support to end users.

The development of the NBS (NIH Business System) is elemental to supporting periodic reporting requirements and to amass the vast amount of transactional data that the NIH generates on a daily basis. This system will assure uniform fulfillment of the legislative requirements under the CFO and GMRA Act and the OMB. Once the system is fully deployed, reviewing the efficacy of the 'General Ledger', 'Budget' and 'Travel' performance in conjunction with the other modules will be an important step towards measuring the achievement of these goals.

DHHS currently has a goal of deploying e-Travel throughout the Department by FY. 2006. The intent is that the e-Travel system will provide functionality, integration with financial components and real-time support similar to that currently implemented by NIH. The NIH is currently analyzing the actions and resources necessary to include NIH travel needs into the consolidated eTravel system, while mitigating disruption or degradation to NIH travelers and administrators. The cost of this integration effort is not included in the FY 2006 funding contributions.

The NBS roll-out phase will support integration activities to UFMS finance systems. The DHHS has scheduled commencement of the NIH/NBS integration with the UFMS General Ledger for FY 2006 and completion by FY 2007. This activity will support the Department's financial integration goals and also meet the President's Management Agenda, "Improving Financial Management". The NBS/UFMS

integration will meet core JFMIP financial management functions across HHS, strengthen internal financial controls and improve the timeliness and accuracy of financial management information.

PERFORMANCE MEASURES		FY 2004				
Deploy and implement modules of the NBS:						
Deploy the general ledger/budgeting module.	(FY02) NBS without general ledger/budget module	•				
Actual Performance: (MET) General ledger/budgeting module deployed.						
Deploy the travel module. FY03 Program steps a-i	(FY02) NBS without travel module	•				
Actual Performance: (MET) Travel module deployed						
Deploy the property module.	(FY02) NBS without property module	O : ->				
Actual Performance: (EXT) Extended to February 2005, after which goal reporting will be covered by target 4.						
Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' FY06 Program steps h-I 'Final review'	(FY03) NBS without contracts/acquisition/accounts payable and receivable /supply modules			o	o	
FY 04 *Actual Performance:* (MET) Completed system design and configuration, unit beta testing and commenced CRP1 testing.						
FY 05 *Actual Performance* : Performance results will be reported in February 2006						
Actual Performance : Performance results will be reported in February 2007						
Deploy the service and supply fund activities module. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' FY06 Program steps h-I 'Final review'	(FY03) NBS without service and supply fund activities module		•	o	o	
Actual Performance: (MET) Identified solutions for automated amortization for Real Property and Agency Agreements.						
Actual Performance : Performance results will be reported in February 2006						
Actual Performance : Performance results will be reported in February 2007						
Report critical elements of General Ledger and Travel Module performance	(FY04) NBS performance with General Ledger and Travel Modules deployed				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met -> Target Extended X Target Not Met

SUMMARY OF **FY 2004** PERFORMANCE RESULTS

Targets 4 and 5. The target in FY2004 was met. The NBS completed system design and configuration, unit beta testing and commenced CRP1 testing. The NBS has also established a baseline training and communication plan that supports workforce transitions. The property and contracts/acquisition/accounts payable and receivables/ supply modules are being re-planned for FY 2006. The purchased software for Property and Contracts/ Acquisition/ Supply modules was originally developed as a commercial off-the shelf product. These applications were judged to need further development for NIH to be compliant with Federal and departmental regulations and policies. Such a delay will mean a continuing use of legacy systems, maintaining complex interfaces with legacy systems, and delaying the full integration of the NBS system.

The NBS project team is proposing an adjustment to the project schedule for the implementation of the supply-chain module to ensure that accurate target dates are developed and ultimately met.

The target in FY2004 was met. The NBS has identified two Service and Supply requirements, Agency Agreements and Real Property management, for deployment prior to the Service and Supply full deployment. The NBS plans to leverage the Oracle purchasing and Project Accounting functionality to meet the Agency Agreement requirements. The Real Property management requirements will be fulfilled with Sunflower property management functionality. These two solutions will provide the finance community with functionality two years before the planned Service and Supply module.

The property and supply chain NBS framework (e.g., layout, design, and table shells), requirements traceability matrix and to-be process designs has been developed for the planned functionality and solutions have been developed to answer and conclude open process issues. Solutions for additional functionality will be added after deployment, as they are completed.

The NBS is partnering with NIH Acquisition re-structuring efforts (ARAC) to assure a consistent integration strategy and meet the NIH re-structuring goals. The aim of this coordinating activity is to maximize the impact of these complementary initiatives.

Implementation Strategy Advances or Other Highlights. The NBS has developed a solution to automate and link the DHHS EHRP to the NBS Human Resources database for all employee based transactions. This information is used to support portal access, travel manager transactions and review and approval processing flows. This solution has been adopted by the UFMS for their organization and people data base needs.

The NIH provided substantial training to support the deployment of the General Ledger and Travel modules of NBS. For NBS Travel, NIH provided pre-deployment training to 2,050 users in about 130 sessions. In addition, it provided post-deployment training to another 584 users. For NBS General Ledger, NIH trained 69 finance personnel and 89 budget personnel.

The NIH established the NBS Management Center in September 2003. The center assists users experiencing difficulty with the NBS modules deployed to date. It also manages the evaluation of user feedback and executes proposed enhancements for the deployed software. The center has established and executed standard escalation protocols for assisting users who are experiencing difficulty, which will inform user training through "lessons learned" and form the backbone of the NBS post-deployment user support, potentially assisting about 6200 users compared to the travel deployment for 2050 users.

The NIH Travel Manager is now used daily by all NIH Travel administrative personnel. Over 180,000 records have been processed in the NBS Travel module. The NBS has improved the travel planner efficiency by providing monthly updates of the GSA and State Dept. rate schedules via an automated upload of current information from the Gelco Travel Manager 'Customer Support' website. Using this feature, new rates are placed directly into the GELCO Travel Manager database. This ensures all standard per diem rates, mileage rates; M&IE deductions and the State/Country tables are updated with current data.

For FY 2004, 182,048 travel authorizations and voucher transactions were entered online in real time; into the Gelco Travel Manager compared with all FY03 transaction being batched and processes from the ABD into the accounting system nightly.

The NBS updates patient records every 5 minutes, seven days a week, for 4,319 patients during the fiscal year. This automated process enables Clinical Center staff to enter patient records and create

corresponding patient travel authorizations within a 5 minute timeframe. This synchronization of patient data enables the Clinical Center to enter and travel patients without manual intervention.

The NBS conducted general ledger mapping and account reviews as part of earlier target activities which virtually eliminated the need for most top side adjustments to correct accounting errors or compliance issues. In FY 2004, corrections to the SGL mapping on 344 distinct transaction types resulted in the correct coding of treasury SGL's on approximately 10 million transactions processed via the legacy system. In FY 2004, approximately 2.5 million SGL compliant obligation records were processed by the NBS, compared with non-compliance a year earlier.

Efficiency.

Data Interfaces

The automation of Human Resource Organization and Employee data loads ensures consistent information between HR, payroll and NBS databases and supports e-government requirements for single data repositories. With over 3,500 NIH organizations, the automation of this manually intensive data entry process has saved and will save over 200 FTE hours per year and minimize the risk of incongruent or missing data between source systems and the NBS. This code is one of the NBS vertebrae; every financial transaction relies on this information. The Department's Unified Financial Management System adapted the code for their organization identification.

GL transaction cleansing

Prior to deploying the Oracle General Ledger, an extensive effort was put into making non-compliant SGLs Treasury compliant. This general ledger mapping and account reviews conducted as part of the tracks 1 and 2 process virtually eliminated the need for most top side adjustments to correct accounting errors or compliance issues.

In FY 2004, NIH corrected the SGL mapping on 344 distinct transaction types that resulted in using the proper Treasury SGLs on almost all 10,000,000 transactions processed via the legacy system. As one example of the success in mapping cost elements, in FY 2003, over 2.3 million obligation transactions (T/C 050) were processed; of which none were SGL compliant. In FY 2004, approximately 2.5 million obligation records were processed and were SGL compliant.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

After careful review of the GAO audit of the Department's UFMS project, the NBS data conversion strategy and the NBS project plans, the NBS has scheduled additional testing activities to assure system viability and acceptable product delivery. In reviewing the proposed delivery schedule, it has been decided to suspend the reporting of activities under track 3 beyond FY04, to avoid duplication of goals in this submission, and to place the reporting of such activities under track 4.

The FY 2006 funding reflects this integration activity with additional funding of $12 million over the original NBS FY 2006 level of $23.004 million for a total level of support of $35.004 million or a 60% increase compared to the NBS 5% increase over the FY 2005 funding.

CBRR-3) STREAMLINE BUSINESS PROCESSES AND AUTOMATE DATA MOVEMENT BY IMPLEMENTING, MONITORING AND UPDATING THE CLINICAL RESEARCH INFORMATION SYSTEM **(CRIS).** (ONGOING)

BACKGROUND

The NIH Clinical Center has been a pioneer in the use of computer technology for the advancement of research and the improvement of care. The present Medical Information System (MIS) was implemented in 1975 and gave NIH physicians access to tools such as physician order entry and a point-and-click interface that are still not implemented in many academic health care settings. Unfortunately, the system was built around a proprietary database, and its capabilities no longer meet the needs of the institution for providing data in both the research and clinical care settings. For some functions such as pharmacy, surgical services, and consent management, no automation is currently in place.

To address the limitations of the present system and to fully automate clinical care information, NIH has embarked on the CRIS project. Specific functionality that will be provided by the CRIS includes:

- Compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and regulations of the Privacy Act of 1974
- Interfacing with ancillary systems to provide integrated data and eliminate paper-and-pencil transfer of data among systems
- Reduction of potential medical errors through the implementation of a pharmacy and surgical scheduling, management, and documentation system
- Management and display of radiologic, anatomic, pathologic, and ultrasound images and other image-based data
- Interfacing to IC research databases
- Support for standardized medical vocabularies
- Support for analyzable electronic documentation (i.e., physician notes)
- Support for protocol-based provision of care
- Provision of management information for resource allocation and cost attribution
- Provision of longitudinal patient data
- Provision of historical patient data for research analysis
- Comprehensive support for patient appointing
- Support for bed management
- Support for nurse acuity assessments

Rationale

Historically, research data have been recorded in stand-alone systems or on paper. Because these research data could not be provided directly from the hospital system, they were typically copied from hospital system computer screens into the local electronic or paper-based research record. Such a process, when multiplied over the research enterprise of NIH, represents a substantial loss of productivity and a major risk of error. Implementation of the CRIS will reduce the life-cycle costs of these clinical information technology projects and obviate the need for IC-specific systems.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

CRIS includes several functional modules that will be phased in once they are completed. The core hospital system will be developed to include modules that streamline business processes and automate data movement among multiple systems. Staff time for redundant data entry will be reduced with the implementation of the core system during FY 2004. In FY 2005, a surgery and anesthesia management system as well as an augmentation of the pharmacy system and patient registration system will be implemented facilitating records management for Clinical Center staff. Additionally, a clinical data warehouse will be developed and used across NIH. The warehouse will directly support the PMA goals of expanded electronic government and improved financial performance. The CRIS project represents the nucleus of clinical informatics for NIH, with the goal of collecting clinical information for patient

care and research in one place. For centralized reporting and monitoring, the completed system will serve as a model for other health care organizations. The new goal for FY 2006 addresses the integration of clinical data systems across the Clinical Center and the NIH to help achieve the goal of collecting data centrally. Working together with CIT to identify multiple clinical systems, ensuring compliance with CHI standards, HL7 compliance and interoperability will ensure meeting the larger goals of the NIH Roadmap and DHHS.

The current CRIS project has delineated to OMB a five-year implementation strategy beginning in FY 2002 and entering a steady state phase after 2006. As with any information system, maintenance includes continual software upgrades and enhancements to ensure the best possible utilization and efficiency of a software system. The CRIS project will continue to add functionality in 2007 and beyond using existing resources within the Clinical Center and through maintenance contracts established through the acquisition and implementation phases of the project.

The development of the CRIS (Clinical Research Information System) is key to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). It is an ambitious undertaking and requires a number of enterprise process and system changes to deliver the long-term goal. The integration, in FY 2006, of clinical systems across NIH intramural programs (to eliminate redundancy) is a key milestone to successfully fulfill the requirement of cross-NIH standardization.

H U H PERFORMANCE MEASURES	BASELINE				
Implement modules of the CRIS:					
Implement a core hospital system	(FY03) 28 year old legacy system				
Actual Performance: (MET) The core hospital system, CRIS, went live and the legacy system was retired.					
Implement a surgery and anesthesia manag;ment system.	(FY03) No current system exists			o	
Actual Performance: Performance results will be reported in February 2006					
Implement a clinical data warehouse.	(FY03) No trans-NIH clinical data warehouse currently exists			o	
FY 05 *Actual Performance:* Performance results will be reported in February 2006					
Integrate clinical systems across NIH intramural programs to eliminate redundancy	(FY 04) Multiple redundant clinical systems exist				o
Actual Performance: Performance results will be reported in February 2007.					

O Target Active • Target Met Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The FY2004 goal was met. The goal of implementing a core hospital information system was realized on August 22, 2004 when the CRIS system went live, on time and on budget. The 28 year-old system for medical orders, results retrieval and clinical documentation was retired and clinicians now have access to a robust clinical system for the provision of patient care and for the collection of research data.

Efficiency. Time savings achieved through the implementation of the CRIS core system reduced time for the entry of complex orders. Using a equivalent group of fellows receiving initial training in the legacy system (MIS) and the new system (CRIS), those entering orders into CRIS system were able to

decrease patient-order entry time by 16% (which presents a 6 minute decrease, from 40 minutes to 34 minutes) for each complex order set.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

The FY 04 target of implementing a core hospital system remains. Initially the FY2004 goal included the implementation of separate modules for pharmacy and scheduling. Given software constraints from the vendor, support for the pharmacy was built into the core system rather than implemented as a separate module. Additional incremental support for the pharmacy will be added throughout FY 05. Scheduling and resource management also are integral to the current implementation and therefore are included within the core hospital system.

CBBR- 4 PROVIDE GREATER FUNCTIONALITY AND MORE STREAMLINED PROCESSES IN GRANTS ADMINISTRATION BY DEVELOPING AND MONITORING THE NIH ELECTRONIC RESEARCH ADMINISTRATION **(ERA). (ONGOING)**

BACKGROUND

The eRA is NIH's infrastructure for conducting interactive electronic transactions for the receipt and review of applications, and the monitoring and administration of NIH grant awards to biomedical investigators worldwide. Public Law 106-107 requires Federal agencies to migrate from paper-based to electronic systems, thus improving the delivery of services to the public. Therefore, the overall objective of the eRA is to provide a two-way electronic interface for the submission and processing of grant applications and reports in compliance with Public Law 106-107. eRA system development incorporates government wide standards and will integrate with the other NIH, DHHS, and e-grants systems. DHHS is the agency partner in the development of the government-wide Grants.gov effort. NIH eRA staff is also involved in this effort. Recently, DHHS designated eRA as the common system for all DHHS research grant processing.

Future eRA aims include the development of methodologies to electronically receive grant applications as extensible Markup Language (XML). XML is the next generation beyond Hypertext Markup Language (HTML), and provides independence from proprietary development tools. XML enables a single data entry point, more efficient maintenance, and higher quality products. This places the NIH eRA system in a strategic position to integrate with the DHHS e-Grants storefront initiative, and ultimately to achieve the ability to execute end-to-end electronic processing between NIH and the external community using shared electronic resources.

Other future eRA aims include the transition of client/server applications to the Java 2 Platform, Enterprise Edition (J2EE) architecture. J2EE enables a component-based, multi-tier enterprise architecture, improving the reusability of eRA assets, and increasing software quality, application reliability, and security. This places the NIH eRA system in a strategic position to become the DHHS grants administration system for all research and training grants.

Existing eRA applications are being migrated to the J2EE-based technology in a systematic manner as defined by an eRA J2EE migration plan. The X-Train system, which is scheduled for migration to the new technology in FY 2004, will expand the ability to monitor training appointment information, and to establish a link to the professional profiles of all NIH trainees.

The DHHS has designated eRA as a Center of Excellence and directed the DHHS Operating Divisions (OPDIV's) to migrate to eRA for processing and tracking their research grants. The consolidation of the research grants processing into one system (eRA) will streamline the research grants administration processes across the Department and will result in greater efficiencies and cost savings within the Department. The Agency for Healthcare Research and Quality (AHRQ) has been using eRA for several years. The OPDIV's that will be using eRA in the future are the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA), and the Health Resources and Services Administration (HRSA).

Rationale

A significant goal for eRA is moving internal work flows from paper-based business processes to electronic processes. With full implementation of the electronic submission and receipt of grant applications nearly completed, an effort is underway to allow electronic access and updating of the application and the data required to administer the grant from application through close out of the grant. One of the first steps in the Internet Assisted Review, which allows reviewers to access and comment on the applications on-line and eliminates making multiple copies of applications for the different reviewers. Financial and progress reporting will be done electronically in the future, and by the end of FY07 or FY08 it is anticipated that most aspects of the grant administration process will be done electronically, which will increase the efficiency of the process and lower the costs.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Electronic reporting will be implemented in institutions participating in the Federal Demonstration Partnership (FDP) through a Web-based progress-reporting system. A pilot of this system began in November 2002, and was tested throughout FY 2003 by making it available to FDP institutions that requested to use it. After ensuring acceptable performance of the progress reporting system once all FDP institutions have been invited to use it, its availability will be expanded to all grantee institutions. This will be publicized as a formal announcement on the NIH Commons during the third quarter of FY 2004. The XML language will be pilot tested by receiving simple, competing grant applications from the grantee community as XML documents. Although the XML pilot supports only a small subset of the types of grant applications received by NIH, it enables NIH to begin establishing the technology infrastructure needed for more complex services, such as those involving multi-project mechanisms. Multi-project progress reporting will be tested by expanding the grant application XML pilot to support complex services, such as the receipt of multi-project progress reports as XML documents.

Migration of existing client/server applications will be completed by implementing an eRA J2EE Migration Plan. This plan stages the transition of proprietary client/server applications to a standard, multi-tier, component-based technology. The J2EE architecture compliments the XML technology, transforming eRA into an open, secure enterprise system.

The implementation strategy is to identify the OPDIV requirements and determine whether the adjustments required by eRA and the OPDIV's in their business processes fit the eRA business process model. The solution is likely a combination of the two approaches. The eRA team will identify change requirements and additional processing capacity in the latter part of FY04, and begin system modifications and testing of new OPDIV processing in FY05. Full processing by eRA for the new OPDIV's will occur during FY06; which is dependent upon the time required for testing and conversion of historical data from current systems.

The transition from a paper-based business process to fully electronic processing has been a vision for the eRA 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 most of the conversion is completed. 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 individual pieces that comprise end-to-end processing of grants. NIH plans to achieve most of this effort by FY08 or FY09. eRA continues to map electronic processes to existing business models, but as these continue to change, eRA efforts will require greater adaptability. These unknowns make it difficult to commit to a specific schedule for completion of paperless processing. Each year the NIH expects the capability for paperless processing to expand and this progress will be reported.

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. To integrate, in FY 2006, OPDIV (DHHS Operating Divisions) with the NIH in full may require adjustments to eRA in the processing and tracking of research grants.

PERFORMANCE MEASURES [1] *Note: Annual targets are grouped by activity.*		FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Develop methodologies to electronically receive grant applications as XML files:							
Implement electronic reporting with all 65 newly online institutions participating in the Federal Demonstration Partnership.[1]	(FY99) No institutions using electronic reporting						
Actual Performance: (MET) Electronic reporting available to the 65 FDP participating institutions.							
Begin pilot-testing of progress reporting for multi-project mechanisms.[2]	(FY99) 14 simple competing grant applications received		-	-			
Actual Performance: (EXT) XML development needed. Extended to 2005							
Expand availability of electronic progress reporting to all grantee institutions.[3]	(FY02) 145 FDP institutions given access to electronic reporting	o	•				
Actual Performance: (MET) 2,800 progress reports electronically and 102 grantee organizations are now registered to submit.							
Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 Goals: FY05 - 25% electronic business processing FY06 - 40% electronic business processing	10% of business processes being done electronically			o	o		
Actual Performance: Performance results will be reported in February 2006							
Actual Performance: Performance results will be reported in February 2007							
Pilot-test extensible Markup Language (XML) transmission between extramural community and NIH.	(FY03) Need for system to conform with OMB/Federal Enterprise Architecture		•				

[1] Target was carried over from previous eRT goal and was met for FY 2003.
[3] Target was carried over from previous eRT goal and was extended for FY 2005.
[2] Target was carried over from previous eRT goal and was extended to FY 2004.

PERFORMANCE MEASURES *Note: Annual targets are grouped by activity.*	BASELINE				FY	FY	
Actual Performance: (MET) Pilot-tested XML transmissions successful and technology incorporated into eRA architecture stack.							
Integrate OPDIV's into eRA							
Develop plan to integrate OPDIV's	No Plan for OPDIV Integration						
Actual Performance: (MET) eRA has developed plans for adding the FDA and components of the CDC.							
Integrate HHS OPDIV's as eRA users for administration of research grants by the end of FY2006. Goals: FY05 - 50% of eligible HHS OPDIV's FY06 100% of eligible HHS OPDIV's	Integration plan has been developed. Limited use of eRA Grant System by two other HHS OPDIV's, AHRQ and CDC/NIOSH			o	o		
Actual Performance: Performance results will be reported in February 2006.							
Actual Performance: Performance results will be reported in February 2007							
Migrate Oracle forms applications into Java Version 2.0 Enterprise Edition (J2EE) technologies:							
By the end of FY 2007 complete migration of existing client/server applications to Web-based technology.[1] Goals: FY05 - 50% code conversion FY06 - 75% code conversion FY07 - 100% code conversion	(FY03) Migration plan developed. Current architecture is client-server mix with web			o	o		
Actual Performance: Performance results will be reported in February 2006.							
Actual Performance: Performance results will be reported in February 2007							

O Target Active • Target Met Target Extended ° Target Not Met

Summary of FY04 Performance Results

Target. The FY2004 target (1) was met. eRA/ NIH have accepted over 2,800 progress reports electronically and 102 grantee organizations are now registered to submit. eCGAP and grants.gov both have been utilized for entering applications electronically in pilot form and the systems changes are in place for eRA to allow all institutions to file process reports electronically.

The FY2004 target (2) was met. XML transmissions between the extramural community and NIH have been successfully tested and integrated into the eRA architecture stack.

The FY2004 target (3) was met. Plans were developed to integrate OPDIV's from both the FDA and components of CDC.

Implementation Strategy Advances or Other Highlights. The eRA program, having successfully tested XML transmissions, has proceeded further with XML as the method for data interchange and has been instrumental in meeting target 1 above due to the speed and success rate of the testing regimen.

Efficiency. Having planned the integration of HHS OPDIV's, NIH was able to accelerate the actual integration, which resulted in 25% of eligible users being placed on the eRA system; not due to start

[1] This target was includes the deployment of the 2.0 version of X-Train, a target that is carried over from previous research training goals.

until FY2005. Communications have been broadened as part of the program cross-talk, between NIH, FDA & CDC (OPDIV integration)

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

FY05 through FY06 targets have been consolidated into three (3) multi-year targets, with specific yearly goals. The performance goals are discussed further in the planned implementation strategies section. This change initiates the alignment of the eRA GPRA targets with those reported on the OMB300, Section I.C. Performance Goals and Measures.

Strategic Management of Human Capital

Performance-based results have become a central theme in human capital management efforts at NIH. NIH is developing a strategic, performance-based approach to workforce management by generating performance goals and measures that will (1) align individual performance with organizational goals, (2) provide seamless leadership continuity and succession planning, and (3) appropriately allocate rewards and incentives.

NIH values employees as an essential organizational asset and strives to provide them with the tools they need to be successful. The workforce plan is designed to match the right person with the right job by ensuring more efficient and effective recruitment, training, and retention. In high-performing organizations, employees see a direct connection between their work and accomplishing the organization's mission. Toward this end, NIH places a heavy emphasis on the education, development, and training of its employees. The plan will enable employees and managers to identify training and career development needs, link training with performance goals, provide meaningful performance incentives, and foster a diverse workforce.

To meet the challenge of workforce management, NIH has delayered management levels and consolidated human resource management functions. In addition, NIH has achieved great success in reaching competitive sourcing goals in a variety of commercial areas. While all these initiatives are under way, NIH managers are confronted with the need to balance the certainty of short-term requirements with long-term planning. In April 2003, the NIH Director formed the Administrative Restructuring Advisory Committee (ARAC) in response to Administration mandates to examine consolidation and restructuring as a means to provide more responsive, flexible, and efficient administrative services. NIH leadership prepared a restructuring and implementation plan, facilitated by NAPA (National Academy for Public Administration), with specific attention paid to the potential for restructuring administrative management functions. In order to meet the challenges set forth, discussions are currently underway to combine elements of ARAC performance targets with milestones into current GPRA goals and associated targets.

The table summarizes the performance goals and due dates included in this section:

Strategic Management of Human Capital	
SMHC-3)	Improve the strategic management of NIH resources by developing and monitoring a comprehensive human capital plan based on the Agency's programmatic objectives and projected future needs. (Ongoing)
SMHC-4)	Ensure that NIH commercial functions are performed as efficiently and cost-effectively as possible by conducting competitive sourcing reviews on the required number of functions within the Agency's commercial inventory. (Ongoing)
SMHC-5)	Improve and monitor the use of Human Resource Services by providing Real-Time Access to Tools via the NIH Portal. (Ongoing)

SMHC- 3 IMPROVE THE STRATEGIC MANAGEMENT OF **NIH** HUMAN RESOURCES BY DEVELOPING AND MONITORING A COMPREHENSIVE HUMAN CAPITAL PLAN BASED ON THE AGENCY'S PROGRAMMATIC OBJECTIVES AND PROJECTED FUTURE NEEDS. **(ONGOING)**

BACKGROUND

The first item on the President's Management Agenda (PMA) is the strategic management of human capital, which seeks to create a more effective Government that depends on attracting, developing, and retaining top-quality employees from diverse backgrounds and ensuring that they perform at high levels. Strategic human capital management is the transformation of how to employ, deploy, develop, and evaluate the workforce. It focuses on results, not processes. It places the right people in the right jobs to most effectively perform the work of the organization.

Rationale

NIH is deeply committed to creating and sustaining a trained and motivated workforce to carry out the mission of the Agency and has taken a number of major steps to improve human capital management. NIH staff developed an initial strategic workforce plan; drafted a transition strategy to re-train and ultimately assign-employees who are not placed in new organizations as a result of competitive sourcing initiatives; consolidated human resource management functions; developed a major initiative to assess and modify the NIH infrastructure of key NIH administrative-management functions; implemented performance contracts for senior executives and managers; and initiated a major effort that will result in recommendations for improving the effectiveness of recruitment, development, and succession planning processes for key scientific positions within the NIH Intramural Research Program. The ongoing study of key positions within the NIH Intramural Research Program will provide a potential framework for the initiation of a future study of key positions within the NIH Extramural Research Program during FY 2006. All of these major activities demonstrate an unwavering commitment on the part of the NIH to the principles behind the PMA and DHHS management initiatives.

Ultimately, the strategic human capital management plan will capture the workforce needs based on NIH's scientific agenda, identify areas of staff expansion and contraction, address competencies and/or success profiles for key NIH Intramural and Extramural positions, incorporate succession planning and leadership development programs to ensure that viable candidates are available for critical positions, and fully integrate human resources policies to shape the NIH workforce according to the mission and direction of the Agency.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Key activities are underway to achieve the FY 04 through FY 06 targets, improve the strategic management of human resources, and aid in the development of a comprehensive human capital plan. The NIH staff is conducting a major study of key positions within the NIH Intramural Research Program (IRP), to include the identification and evaluation of industry best practices related to key IRP positions; development, piloting, conduct, and analyses of incumbent interviews regarding current IRP succession planning processes and systems associated with eight categories of key IRP positions; development of competencies or success profiles of eight roles and four tiers of key IRP scientific roles; analysis and comparison of incumbent interview/competency criteria to industry best practices; and validation of the IRP competency model. An assessment of NIH strengths and weaknesses regarding succession planning for key IRP positions will be conducted considering the scientific agenda and future workforce needs. A study of key IRP positions will be conducted to determine dynamics of the positions and associated competencies; gaps in positions will be identified; and an assessment of the gaps will establish future impact. An additional framework of quantitative and qualitative information related to key IRP positions will also be derived from the conduct of annual studies of average age, years of service, retirement eligibility, retention, recruitment strategies and activities, and points of concern about the recruitment and selection processes. Findings from major and annual studies will be utilized to improve the strategic management of human resources. An associated system of performance indicators will be established to assess human capital management of key positions within the IRP.

An implementation plan will be developed to address the most significant challenges, gaps, policies, and systems needed to improve recruitment, development and succession planning processes for key IRP positions. Human capital needs of key positions within the NIH Intramural Research Program will be projected for 3 to 5 years. Findings, conclusions and initiatives will be incorporated into the NIH strategic workforce plan and other programmatic documents.

It is anticipated that the IRP human capital initiatives will serve as an initial framework for an overlapping study of key NIH Extramural Research Program positions while an assessment of newly instituted IRP methods is being accomplished. Additionally, NIH is currently co-chairing a Department-wide initiative to develop a leadership competency model and design competency based training and development opportunities for HHS leaders.

PERFORMANCE MEASURES	BASELINE					
Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.	(FY 01) NIH Workforce Plan, June 2001.		•			
Actual Performance: (MET) Recommendations were identified, as potential initiatives, for improving human capital management; in key Intramural Research roles.						
Conduct a study to identify competencies needed by NIH leaders who will drive future development efforts.	(FY 02) Administrative Restructuring Advisory Committee.					
Actual Performance: (MET) A major study to identify competencies and success profiles of key Intramural leaders was completed.						
Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.	Performance indicators to be determined from FY 2004 results.			o		
Actual Performance: Performance results will be reported in February 2006.						
Establish performance indicators with baselines related to recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.	Performance indicators to be determined from FY 2004 results.			o		
Actual Performance: Performance results will be reported in February 2006.						
Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Extramural Research Program.	(FY 04) Performance indicators and additional performance indicators to be determined from FY 2005 results.				o	
Actual Performance: Performance results will be reported in February 2007.						
Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program. (Report on performance indicators and expected enhancements.)	(FY 04) Performance indicators and additional performance indicators to be determined from FY 2005 results.				o	
Actual Performance: Performance results will be reported in February 2007.						

O Target Active • Target Met -> Target Extended X Target Not Met

SUMMARY OF **FY04** PERFORMANCE RESULTS

Target. The FY2004 targets were met. Planned studies were completed to, (1) identify a number of recommendations for improving human capital management processes for eight key Intramural Research roles, and (2) to identify competencies and success profiles of key Intramural leaders who will drive future development efforts.

Efficiency. The studies were completed ahead of schedule, which enabled the program team to determine methods derived from recommendations and begin the roll-out and measurement activities scheduled for FY2005..

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS.

The previous submission included Goals b and c under Strategic Management of Human Capital. During the development and conduct of studies in the area of recruitment, development and succession planning for key scientific positions within the NIH Intramural Research Program, it was determined that Goal b contained only some of the fundamental criteria that was essential to the scope of work being conducted in the Intramural Research Program.

Goal b was analyzed to be limited in scope, as it focused on "critical leadership", compared to the broader approach of studying "key scientific positions" within the NIH Intramural Research Program. It is anticipated that the expanded approach of studying "key scientific positions" rather than "critical leadership positions" will enhance the ability of NIH staff to improve key aspects of recruitment, development and succession planning activities that are cross-cutting to many more activities within the NIH. The ongoing study of key positions within the NIH Intramural Research Program will provide a potential framework for the initiation of a future study of key scientific positions within the NIH Extramural Research Program during FY 2006.

SMHC- 4 ENSURE THAT **NIH** COMMERCIAL FUNCTIONS ARE PERFORMED AS EFFICIENTLY AND COST-EFFECTIVELY AS POSSIBLE BY CONDUCTING COMPETITIVE SOURCING REVIEWS ON THE REQUIRED NUMBER OF FUNCTIONS WITHIN THE AGENCY'S COMMERCIAL INVENTORY. (ONGOING)

BACKGROUND

Governed by OMB Circular A-76, the underlying goals of the competitive sourcing initiative are to:

- Increase competition, thereby generating savings and noticeable performance improvements.
- Promote innovation, efficiency, and greater effectiveness through competition.
- Provide an imperative for the public sector to focus on continuous improvement by focusing on desired results and outcomes and removing roadblocks to greater efficiency.

In support of the HHS objectives and the President's Management Agenda (PMA), NIH began identifying commercial activities for competitive sourcing reviews in FY 2002. NIH plans to perform cost comparisons on 100% of its commercial activities. These will be completed according to the requirements provided in the future years.

The competitive sourcing program will ensure that commercial activities are subjected to the rigor and discipline of market competition. On completion of each comparison, NIH will select the source that can provide the necessary services and ensure that quality standards are met at the lowest possible price.

Consistent with the Department's commitment that affected employees will have a job, NIH will be using all tools at its disposal to retrain, counsel, and place affected employees within NIH, HHS, other federal agencies or alternate employers. Use of VERA and Voluntary Separation Incentive Payments should help reduce the number of affected employees who will need to be placed.

Rationale

The HHS views competitive sourcing as a method to "achieve excellence in management services and thereby improve overall Department management," (goal number 8 in the HHS strategic plan). Like consolidation and centralization, improved financial management, and electronic commerce, competitive sourcing aims to improve efficiency, in order that HHS may more effectively deliver health and human services. For this reason HHS has taken a highly strategic approach to institutionalizing competitive sourcing - one that carefully reflects the needs of the Department.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

In accordance with the PMA, NIH plans to carry out annual commercial sourcing reviews. The bases for the reviews are the number of full time equivalent staff in particular functional areas and the annual guidance from the Department. To accomplish this task each year, NIH carries out a preplanning step in order to identify potential functional areas for review. Subsets of the identified functional areas are then deemed appropriate for review through a negotiation process with the Department and OMB and then are reviewed. The A-76 requirement is met once the reviews are conducted and awards are made.

For FY 2004, the preplanning step identified 14 potential functional areas for review, and of these, eleven were deemed appropriate for review. To date eight reviews have been conducted.

After each review is completed, NIH will develop transition plans to move to the new organizational structures and fill positions as proposed in the respective Most Efficient Organizations (MEOs) awards. For FY 2004 the NIH Transition Center delivered career transition services to employees impacted by the two FY 2003 competitive sourcing studies. In FY 2005, an evaluation of those services will be performed; thereby, concluding the implementation of services. Consequently, this performance target will terminate in FY 2006.

PERFORMANCE MEASURES	BASELINE					
Identify annually commercial activities for competitive sourcing comparison.	(FY02) Preplanning initiated for identifying functional areas		•	o	o	
Actual Performance: (MET) Extramural Administrative Support Services and Real Property Management groups identified for competitive sourcing comparison.						
Actual Performance: (MET) Nine streamlined and two standard studies conducted in FY 2004.						
Actual Performance: Performance results will be reported in February 2006.						
Actual Performance: Performance results will be reported in February 2007.						
Complete negotiated competitive sourcing reviews annually.	(FY02) Functional areas identified as appropriate for review		•	o	o	
Actual Performance: (MET) Competitive-sourcing reviews completed for Extramural Administrative Support Services and Real Property Management groups.						
Actual Performance: (MET) Nine streamlined studies completed, with 8 work awards placed with NIH.						
Actual Performance: Performance results will be reported in February 2006.						
Actual Performance: Performance results will be reported in February 2007.						

PERFORMANCE MEASURES	BASELINE		FY 2004		
Implement transition services for employees annually displaced due to prior year's competitive sourcing.	(FY03) Transition plans developed for employees		•		
FY04 *Actual Performance:* (MET) Career transition services provided for out-placed staff as a result of competitive assessments/ studies.					
Evaluate transition services provided to employees.	(FY03) Career transition services provided to employees impacted by one of the FY 2003 studies.				
FY05 *Actual Performance:* Performance results will be reported in February 2006.					

^ *Target Active*	• Target Met	Target Extended	X Target Not Met

Summary of FY04 Performance Results

Target. The target (1) in FY2004 was met. Commercial activities were identified and reviews planned for in FY2005.

a. Food Services
b. Medical and Dental Equipment Biomedical Engineer and Industrial Plant Equipment
c. Training - IT Security, Employee Development, Professional Development Training
d. IT Web Site Development and Maintenance
e. IT Data Maintenance Administrative Activities and Computing Services
f. IT Other Information Operations Services
g. Library Technicians
h. Administrative Support and Other Environmental Services Activities
i. Patient Care Unit Clerks

The target (2) in FY2004 was met. Eleven competitive sourcing reviews were undertaken as part of ongoing activities. Of the 11 studies, nine were judged (under A-76) as warranting a "streamlined" study due to the size of the agency/ entity in questions.

AREA	STUDY TYPE (A76 GUIDANCE)	RESULT
IT Telecommunications	Streamlined	won
NIEHS Logistics	Streamlined	won
Clinical Center Materials Management	Streamlined	won
Freight Forwarding	Streamlined	won
RML Logistics	Streamlined	won
RML Visual and Medical Arts	Streamlined	won
IT Help Desk	Streamlined	won
IT Data Center	Streamlined	won
IT Voucher Examiners	Streamlined	lost
Logistics Supply and Warehouse	Standard	won
Visual and Medical Arts	Standard	pending

The target (3) in FY2004 was met. Career transition services were provided to employees who (1) lost job duties as a result of one of the FY 2003 studies, and (2) were impacted by other FY 2003 study and the FY 2004 studies.

Implementation Strategy Advances or Other Highlights.
The NIH received a green status rating and 'progress' rating on the President's Management Agenda competitive sourcing initiative; for FY 2004 accomplishments in this area.

Of nine competitive sourcing assessments undertaken (streamlined studies - see table above) the NIH won eight, supporting the HHS strategic plan goal - "Achieve excellence in management practices".

Efficiency. During the performance year the NIH undertook to analyze nine of its service products. The NIH was viewed as most competitive/ effective in the free-market place and therefore work was awarded to the NIH for eight of the nine product comparisons.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target
Although NIH provided career transition services in FY 2004 through the NIH Transition Center to employees impacted by the two FY 2003 competitive sourcing studies, it was not in direct response to requirements of OMB Circular A-76; the basis of SMHC-d. NIH employees do not meet the criteria for the assistance stipulated in that policy, "Assist adversely affected federal employees in accordance with 5 C.F.R. Parts 330 and 351" because they do not meet the definition of "adversely affected" in the cited regulations. In FY 2005, an evaluation of the services will be performed to obtain information that will enable a determination to be made on the necessity of continuing.

Therefore, NIH proposes dropping target 4 in FY 2006 because it does not report information directly related to accomplishment of the goal.

In FY 2005, NIH proposes to complete target 3 by conducting an evaluation of the transition services as stated in target 4 "evaluate the transition services provided to the employees." The actual transition services will be "implemented" in FY 2004 enabling an evaluation in FY 2005. The proposed evaluation will conclude the transition process as referenced in this goal.

SMHC- 5 IMPROVE AND MONITOR THE USE OF HUMAN RESOURCE SERVICES BY PROVIDING REAL-TIME ACCESS TO TOOLS VIA THE NIH PORTAL. (ONGOING)

BACKGROUND
The NIH Portal is the next generation intranet for the NIH community. It employs a document directory to organize loose documents by subject, regardless of source, in one logical taxonomy and can be used as a launch pad for enterprise systems and access to information that pertains to the NIH mission. The Portal uses approximately 100 "gadgets" to launch or interact with enterprise systems such as ITAS, Employee Express and the NIH Manual Chapters database. 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.

Currently, Human Resources information relevant to the NIH community is posted on a variety of websites (OHR, ICs, OPM, HHS, etc.), leading to confusion among users, duplication of effort, and a cumbersome search process. Making the HR Community of the NIH Portal available to the NIH community will give users one-one-stop shopping for relevant HR information, resources and systems.

Rationale

The HR community and other users of HR resources have often expressed frustration when trying to find current, relevant HR information. Subject matter experts have found it difficult to maintain the currency of HR information. The portal technology will allow for distributed content management, so that subject matter experts can take greater control of their documents and content and self-publish them to the HR Community. By making the HR Community of the NIH Portal the primary site for NIH HR guidance, NIH can greatly improve service to users and subject matter experts alike.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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. Their relevance, currency and appropriate placement were considered in determining which ones would be accessible through the Portal. Duplicates and obsolete versions were discarded and the remaining 4,000 to 5,000 documents were categorized in the document directory.

In 2003, OHR assumed management of its own content and committed to launching all new HR systems through the NIH Portal. In 2004, the Strategic Programs Division (SPD), OHR began maintaining these documents by "crawlers," which automatically check their 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. Subject matter experts have merely to review new documents and approve them before they are published to the document directory. OHR has 107 crawlers that check their designated sites nightly.

NIH will develop Target 1 which is to develop an HR Community on the NIH Portal. This will become the primary site for NIH HR information, systems and resources. Target 2 is to identify HR critical elements and tools to monitor use and quality of the HR information. In fiscal year FY 2005, SPD will launch the HR Community area of the NIH Portal, train users on accessing the Portal and the Community, market the Community's availability, and eliminate where feasible and appropriate, access to HR systems, information and resources through means other than the Portal.

Also in FY05, SPD will establish the HR critical elements and identify methods to measure them. For example, assuming usage of the HR Community site is one of the critical elements, SPD will work with CIT to determine methods to greater quantify and define usage as distinct hits on the HR Community site. SPD can then 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.

Target 3 is to establish baselines for the HR critical elements to monitor over time, and. Target 4 is to develop a plan for corrective strategies to improve usability and quality of HR information. In fiscal year FY 2006, the SPD will determine the baselines for the HR critical elements and establish a plan to manage and continuously improve the quality and features of the HR Community.

Building upon prior activities, in building a portal-based Human Resources (HR) system, current goals detail a task to measure the success of the tool in readily providing users with access to HR related policies, publications and guidelines. Current activities explore and establish baselines for the HR system to be monitored over time, with the development of corrective strategies where applicable.

Baseline(s)

- Multiple means of access to HR systems; multiple websites for HR information and resources
- Inconsistent quality and currency of HR information
- HR Community established
- HR critical elements and tools identified.

PERFORMANCE MEASURES	BASELINE					
Develop an HR Community on the NIH Portal to become the primary site for NIH HR information, systems and resources.	(FY04) Multiple means of access to HR systems; multiple websites for HR information and resources			o		
Actual Performance: Performance results will be reported in February 2006.						
Identify HR critical elements and tools to monitor use and quality of the HR information.	Inconsistent quality and currency of HR information.			o		
Actual Performance: Performance results will be reported in February 2006.						
Establish baselines for the HR critical elements to monitor over time.	(FY05) HR critical elements and tools identified.				o	
Actual Performance: Performance results will be reported in February 2007.						
Develop a plan for corrective strategies to improve usability and quality of HR information.	(FY05) HR Community established				o	
Actual Performance: Performance results will be reported in February 2007.						
		!	!	|	|	! |
Actual Performance: Performance results will be reported in February 2008.						
		:	!	:	:	!
Actual Performance: Performance results will be reported in February 2009.						

o Target Active • Target Met -> Target Extended X Target Not Met

SUMMARY OF **FY04** PERFORMANCE RESULTS

Target. Performance results will be reported in February 2006.

Program Oversight and Improvement

NIH takes responsibility as a steward of Federal funds seriously. Exercising careful oversight is key to demonstrating good stewardship. In addition, NIH strives to continually improve oversight procedures, policies, and systems when needed or opportunity arises. Management systems must be repeatedly updated to keep pace with advances in public administration, and mechanisms to ensure proper stewardship must evolve with the development of new requirements and rising thresholds for accountability. Meeting these challenges has always been a priority for NIH, but the PMA and the "One HHS" management objectives are focusing NIH attention even more tightly on results-oriented management.

The philosophy/value of results-oriented management is beginning to permeate oversight practices for all types of NIH activities and at all levels of supervision. Examples include implementation of an Earned Value Analysis and Management System for oversight of construction projects, expansion of the use of performance-based contracting, linkage of employee performance contracts with organizational objectives, and performance of proactive, compliance site visits to grantee institutions.

The table summarizes the performance goals and due dates included in this section:

Program Oversight and Improvement	
POI-1)	Ensure that approved design and construction projects are executed on time, on scope, and on budget, by implementing and monitoring an Earned Value Analysis and Management System. (Ongoing)
POI-2)	Utilize Performance Based Contracting (PBC). (Ongoing)
POI-4)	By 2005, ensure proper stewardship of public funding for research.
POI-5)	*By 2010, enhance NIH's ability to demonstrate benefits for extramural research investments through changes to policy and information system.*

POI-1 ENSURE THAT APPROVED DESIGN AND CONSTRUCTION PROJECTS ARE EXECUTED ON TIME, ON SCOPE, AND ON BUDGET BY IMPLEMENTING AND MONITORING AN EARNED VALUE ANALYSIS AND MANAGEMENT SYSTEM (EVAMS). (ONGOING)

BACKGROUND

NIH is committed to efficient and effective management and oversight of its real property capital projects. The Earned Value Analysis and Management System (EVAMS) will provide a means to do this. EVAMS is a project data analysis framework that links cost and schedule estimates to actual results. Work is planned, budgeted, and scheduled in time-phased "planned value" increments that permit real-time data analysis to determine contract status. This data assists the project manager with forecasting potential problems.

Earned Value Management (EVM) provides an early warning system for deviations from project plans and quantifies technical problems in cost and schedule terms, providing sound and objective basis for considering corrective actions. EVM helps flag and develop strategies to mitigate the risk of cost and schedule overruns while also providing a forecast of final cost and schedule outcomes. The EVAMS will provide NIH Project Managers with a management system, tools and the information needed to improve their ability to manage, report on, track project performance, and intervene as necessary when the risk to successful completion of a project increases.

Rationale

Earned Value Management (EVM) is an integrated project management system that will significantly improve NIH's ability to actively track capital project performance management.

This goal is consistent with the philosophy of the Federal Real Property Executive Order that recommends establishment of clear goals and objectives to improve agencies accountability for real property and with OMB Circular No.A-11, Part 7 that references EVM as a project management system required to support facility budget submissions.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

In accordance with OMB Circular No.A-11, Part 7, NIH will implement a project management review system based on the EVAMS. This will be used to monitor and manage the performance of the design, acquisition, construction, and commissioning of capital facility projects. As a first step in the implementation of the EVAMS, NIH will integrate existing project management data from Lab 33, and the Northwest Parking Garage, into a "proof-of-concept" version of an NIH EVAMS. NIH will use

information generated by EVAMS data reports and analysis to evaluate and redesign work processes to improve the efficiency and effectiveness of its capital project delivery systems.

The NIH established preliminary EVMS policies and procedures in June 2003 as a management tool to improve the delivery of capital projects. Projects in design and proposed for construction were selected to pilot the system and be a source for collection of data to validate its effectiveness and flag areas needing enhancements.

Evaluation and assessment of existing project management systems and their integration into a proof-of-concept version of an EVAMS are estimated to take between nine and 12 months. The first draft of the development of EVAMS policies and procedures began in late June 2003. Implementation of a revised project management system that incorporates EVAMS is expected to take place within 16 months after the evaluation and proof of concept are completed.

Further, NIH will continue review of its project management systems, benchmark with public and private sector organizations, and pursue a grant under the NIH One Percent Evaluation Set Aside Program to assist in the evaluation, assessment, and validation of proposed EVAMS methodology.

Concurrent with this action, Office of Research Facilities (ORF) will begin initial implementation of its proposed EVAMS, beta test the system using a minimum of one (1) design and up to two (2) construction projects, and provide top management and Project Manager level training on the use of the EVM management system to enable better management and facilitation of on time, within scope, and within budget delivery of projects.

The NIH will continue data analysis and collection to enhance the EVMS. The services of a consultant, recognized as an EVAMS specialist, will be obtained to review, analyze and further validate the proof of concept version. Data will be verified using information from the Office of Research Facilities Quality Management System and the earned-value analyses that are performed for pilot projects. The lessons-learned from the pilot test, the benchmark results and the observations of consultants will be used to fully launch the NIH EVAMS in FY 2005.

By the end of FY 2006, conduct Earned Value Analyses for major capital acquisition projects using the information as a baseline for future year analyses.

PERFORMANCE MEASURES	BASELINE	1 1 2003	FY 2004				2008
Evaluate and assess existing project management systems integrating findings for implementation of a proof-of-concept version of NIHs Earned Value Management System (EVMS).	(FY03) Policies and procedures in place to identify data needed for evaluation						
Actual Performance: (MET) Project Management Systems were evaluated and assessed by ORF staff and EVMS external experts.							
Implement a revised project management system that incorporates Earned-Value Analysis and Management principles to evaluate on time and within budget delivery of projects.	(FY03) EVAMS proof-of-concept version						
Actual Performance: Performance results will be reported in February 2006.							1

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004				
Fully launch the Earned Value Management System (EVMS) and conduct Earned-Value Analyses to evaluate and assess major capital acquisition projects included in the NIH Real Estate Portfolio.	(FY05) Earned Value Management System (EVMS) is incorporated into the project management system.						

Actual Performance: Performance results will be reported in February 2007.

O Target Active • Target Met Target Extended X Target Not Met

Summary of FY04 Performance Results

Target. The FY2004 target was met. Project Management Systems were evaluated and assessed by professionals in the Office of Research Facilities and subject matter experts hired under the NIH One Percent Set-aside Program to provide guidance on how to implement an Earned Value Management System (EVMS).

In accordance with the Office of Management and Budget (OMB) Circular No. A-11, Part 7, NIH is implementing a project management review system based on an Earned Value Analysis and Management System (EVAMS) for oversight of it's major capital acquisitions. In June 2003, the NIH developed EVMS policies and procedures as a tool to improve the delivery of capital acquisition projects.

The policies developed have been integrated into the NIH Quality Systems Manual which outlines the Plan-Do-Check-Act cycle inherent to NIH's project management processes. On-going training in the theory, application and integration of an EVMS into NIH's business practices is being provided to senior, program and project level managers. As a result, the NIH initiated two projects to develop a "proof-of-concept" version of the NIH EVMS.

In FY04, ORF professionals and outside subject matter experts assessed various Project Management Systems for their ability to capture real time project data used in earned value analyses calculations and their compatibility with existing business practices, contract mechanisms, project complexity, and level of project assessment that NIH requires. Interviews were conducted with ORF staff involved with the delivery of facilities to identify gaps between current practices and those needed for full implementation of an EVMS.

ORF and its EVMS advisors will continue evaluation of NIH project management practices and procedures, and based on findings, redesign existing work processes for improved efficiency and effectiveness to deliver capital projects on time and within budget.

Implementation Strategy Advances or Other Highlights. The gap analysis undertaken during the assessment and evaluation stage will be used to re-engineer and enhance program and project management practices of the NIH.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

The word "monitoring" was added to the goal to facilitate ongoing performance reporting.

POI-2) UTILIZE PERFORMANCE-BASED CONTRACTING **(PBC).** (ONGOING)

BACKGROUND

One of the major challenges for Federal Government management and administration is improving the efficiency and effectiveness of contracting and procurement activities. Historically, Government policies, regulations, and attention have been directed at acquisition of supplies rather than services. A 1997 OMB memorandum requires that all Federal agencies use 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.

Rationale

The Office of Management and Budget/Office of Federal Procurement Policy (OMB/OFPP) has placed an increased emphasis on PBC. 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, OMB established annual targets. NIH's PBC GPRA goals for FY 2004 and FY 2005 are based on achieving the OMB targets. In a September 7, 2004 memorandum, the OMB stated its plan to reevaluate the target achievement levels for future years based on agencies' FY 2005 Performance.

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.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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 our ability to apply PBC methods to our 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. IC contracting offices are being reminded of the Government-wide move toward increased use of PBC and that PBC is an NIH GPRA target. 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 OMB/OFPP target set annually.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Increase the amount of NIH contracting dollars allocated through Performance-Based Contracting (PBC):							
Allocate $226 million of available NIH contracting dollars to PBC-eligible contracts.	(FY02) $207 million projected for contracted work with requirements tied to performance	•	•JIJIJIJIJIJIJIJIJIJIJIJV				
Actual Performance: (MET) Obligated $557 million of eligible service contracting dollars through performance-based contracting.							
Obligate 40% of eligible service contracting dollars through PBC.	Obligate 40% of eligible service contracting dollars through performance-based contracting.			iIfIIfIIfIIfIIfIIfIIfIIfIM			
Actual Performance: (MET) Obligated $654 million of eligible service contracting dollars through performance-based contracting.							
Obligate 40% of eligible service contracting dollars through PBC.	Obligate 40% of eligible service contracting dollars through performance-based contracting.			o			
Actual Performance: Performance results will be reported in February 2006.							
Obligate FY 2006 OMB/OFPP Goal of eligible service contracting dollars through PBC.	FY 2006 OMB/OFPP Goal				o		
Actual Performance: Performance results will be reported in February 2007.							

o	Target Active	•	Target Met		Target Extended	X	Target Not Met

Summary of FY04 Performance Results

Target. The target for FY2004 was met and exceeded. Total eligible service contracting dollars were $1,427,094,155. Forty percent of this amount is $570,837,662. Obligations to PBC eligible service contracts as reported in the Departmental Contract Information System (DCIS) were $654,005,154, approximately 46% of the total eligible dollars. These obligations were reported throughout the fiscal year as monies were committed to various contracts throughout NIH.

Implementation Strategy Advances or Other Highlights. PBC activity is tracked monthly through submission of reports from the contracting offices and through reports of PBC funding activity to the DCIS. The funds obligated to PBC in FY 2004, $654,005,154, shows considerable movement toward further implementation of PBC from FY 2003, where the amount obligated to PBC was $557,899,153.

Efficiency. The FY2004 target was exceeded, by 6% i.e., a further $80million worth of service contracts were assessed and managed using quantitative and qualitative metrics/ standards.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

For FY 2004 through FY 2006, the target has been recast to make it more outcome-oriented by focusing on percentage of eligible service contracting dollars obligated to PBC. This approach is similar to that taken by OMB and allows the NIH targets to parallel directives from the OMB/OFPP.

The OMB/OFPP will consult with federal agency chief acquisition officials to reevaluate the target achievement levels for future years based on agency FY 2005 performance. The NIH FY 2006 GPRA target will be the same as that set by the OMB/OFPP.

POI-4) BY 2005, ENSURE PROPER STEWARDSHIP OF PUBLIC FUNDING FOR RESEARCH.

BACKGROUND

With the receipt of NIH grant awards or other types of public funding for research, principal investigators and grantee institutions accept the responsibility to conduct scientific studies ethically and honestly and to provide proper stewardship of NIH funds. Because of the nature of the assistance relationship, which is predicated largely on trust between the sponsor (NIH) and the recipient (grantee institution), the need for effective internal and external compliance programs is essential. One of the 10 Department-wide program objectives, "Advance science and medical research," lists as one of its components the strengthening of mechanisms for ensuring the protection of human subjects and the integrity of the research process. Although these are only two of the many research compliance issues of concern to NIH, the Agency complemented the objectives of the DHHS Offices of Research Integrity and Human Subjects Research by supporting and establishing programs in these two areas. NIH support of research on Research Integrity and the Human Subjects Research Enhancements Program are two such examples, and underpin Objective 4.5 in the DHHS Strategic Plan for FY 2003-2008.

Rationale

To minimize the risks associated with noncompliance, NIH established a goal in FY 2001 to ensure proper stewardship of public funding for research. This crosscutting goal involves ICs working in partnership with grantee institutions and national professional organizations to improve institutional compliance with NIH requirements.

Planned Implementation Strategies

A significant NIH strategy for enhancing compliance is to develop a proactive grants compliance program. The program currently focuses on the following major activities: (1) enhancing administrative oversight by creating a new organizational component within NIH with the capacity to perform annual proactive compliance site visits, (2) increasing educational outreach by providing compliance seminars and providing Web-based information and tools to help grantees understand their stewardship role and improve their institutional compliance programs, and (3) creating an internal NIH compliance program to provide management control and exercise oversight for implementation of grant-related policies.

The compliance program will involve a newly established management controls compliance program. A subset of grants administration policies will be reviewed in order to assess the risk level of each policy. After this is accomplished, NIH can begin the internal compliance reviews (now planned for 2004). The latter will help to determine if the policies are correct, clear, and/or if training is needed to address any instances of noncompliance. These activities serve to enhance NIH's oversight of sponsored research. By the end of FY 2005 NIH will have developed an ongoing program for internal compliance reviews which, combined with other continuing efforts, will complete the goal of developing a strong program to ensure proper stewardship of public funding for research.

PERFORMANCE MEASURES *Note: Annual targets are grouped by activity.*	BASELINE		FY 2004				
Enhance NIH's administrative oversight of sponsored research:							
Conduct five proactive compliance site visits.	(FY02) Criteria in place for selecting institutions for site visits						
Actual Performance: (MET) Five proactive compliance site visits conducted							
Perform a risk assessment and develop a plan for reviews of compliance with grant-related policies.	(FY03) Framework in place for risk assessment						
Actual Performance: (MET) Initial risk assessment of 35 grants administration policies performed; ten policies selected for compliance review.							
Provide Internet-accessible resource information and/or tools for implementing institutional compliance programs.	(FY02) Web site in place for grants compliance and oversight under the Office of Extramural Research	•					
Actual Performance: (MET) Internet-accessible resource information posted on enhancing institutional compliance programs.							
Begin internal compliance reviews.	(FY03) Ten policies selected for compliance reviews		•				
Actual Performance: (MET) Compliance reviews grants-administration policies were initiated.							

PERFORMANCE MEASURES *Note: Annual targets are grouped by activity.*	BASELINE		FY 2004				
Implement recommendations from the internal compliance reviews held in 2004. By the end of FY 2005 NIH will have developed an ongoing program for internal compliance reviews which, combined with other continuing efforts, will complete the goal of developing a strong program to ensure proper stewardship of public funding for research.	(FY04) Completed compliance reviews			O			
FY 2011	*Actual Performance:* Performance results will be reported in February 2006						

o Target Active	• Target Met	Target Extended	X Target Not Met

Summary of FY04 Performance Results

Target. The FY2004 target was met. Plans for compliance reviews were developed and grants policy assessments were initiated. The initial review highlighted inconsistencies in the application of one key policy. A plan was developed to document the steps necessary to affect change. To this end, the Division of Grants Compliance and Oversight will commence one-on-one consultations (in FY05) with ICs to discuss ways of enhancing compliance.

The results of the evaluation will be shared (in FY05) with the Grants Management Advisory Committee, an NIH-wide committee of grants management officers from each IC that concerns itself with those activities designed to insure compliance with fiscal and administrative policy requirements, to identify needs for further policy clarification.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

The 2005 target was changed to show that with the implementation of the recommendations, from the internal compliance review, NIH has established on-going programs that will provide the information needed to ensure proper stewardship of public funding for research.

By the end of FY 2005, NIH will have launched a program for internal compliance reviews and implemented recommendations from those reviews, established an ongoing program of management control compliance assessments, made proactive compliance site visits and rigorous outreach programs integral parts of NIH's continuing operations, and have processes in place to continue to make advances in electronic research administration systems development that serve to enhance communications and oversight of the research portfolio.

CHANGES AND IMPROVEMENTS OVER PREVIOUS YEAR

The current Plan/Report contains 37 goals and 47 targets for the FY 2006 Plan; 42 goals and 56 for the Revised Final FY 2005 Plan; and 41 goals and 53 targets for the Final FY 2004 Plan. Of these goals, the majority fall under the Scientific Research Outcome category. Goals in the remaining functional areas (Communication and Transfer of Results; Capacity Building and Research Resources, Strategic Management of Human Capital, Program Oversight and Improvement) address objectives described in the PMA and the management objectives in the One DHHS Plan. These latter goals underscore NIH's commitment to responsible management of its research dollars.

Integration of CJ with GPRA

The Congressional Budget Justification, and the Annual Performance Plan for FYs 2005 and 2006 and the Annual Performance Report for 2004 as required by GPRA, are combined into a single document. Long-

term performance goals and annual performance targets are aligned with resources and displayed in a matrix according to risk and time to achievement. By linking performance to resources, NIH can enhance the management of its vast research portfolio and justify decisions made on programs and budget.

Integration of GPRA with PART

For FY 2006, the NIH Extramural Program underwent PART review. Five Scientific Research Outcome goals, selected to represent the entirety of the NIH extramural research effort, were assessed using PART. The PART score and associated recommendations are trans-NIH. Therefore, a reference is included in the relevant SROs to show linkage to the PART Summary found in the Performance Overview.

Changes/Improvements in GPRA Goals and Targets

Goal identifiers have been changed to improve tracking as goals are achieved and dropped, added or moved to depict the appropriate time frame. The letters were replaced with a decimal point and number. For instance, SRO-1a became SRO-1.1; SRO-4b became SRO-4.2; SRO-8e became SRO-8.5.; CTR-a became CTR-1; and POI-c became POI-3. As the goal moves across time in the matrix, a new position number will be included in the label. For instance, SRO-3.1 will become SRO-2.3.1 which will eventually become SRO-1.2.3.1.

In the SRO section, a number of targets were changed to reflect the most current scientific knowledge and support the greatest likelihood of goal achievement. A Roadmap goal (SRO-8.5) was also added. These changes are described in the table below.

GOAL IDENTIFIER	DESCRIPTION OF CHANGE	PREVIOUS WORDING	NEW WORDING
SRO-1.2	Target adjusted due to insight from ongoing planned evaluations revealed the need for additional steps.	(FY05) Combine the diaphragm and the electronic output circuitry into a directional microphone that is small enough to fit into a hearing aid.	(FY05) Combine the diaphragm and the electronic output circuitry into a directional microphone.
SRO-2.1	Goal end date adjusted due to time required to enroll participants (two years), the length of the trial (five years), and the time necessary to analyze data and publish the results (one year).	By 2007, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies.	By 2013, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies.
SRO-2.1	Target adjusted due to clinical hold of agent to be used in clinical trials.	(FY05) Establish the baseline success rate for islet transplantation, which may impact U.S. Food and Drug Administration (FDA) and Medicare standards of care for islet transplantation.	(FY05) Submit response to FDA addressing safety concerns about anti-CD3 antibody.
	Goal has moved within NIH's matrix, therefore, the goal designation has been changed from "SRO-2.1" to "SRO-3.2.1"	SRO-2.1	SRO-3.2.1
SRO-2.1	Target adjusted due to clinical hold of agent to be used in clinical trials.	(FY06) Analyze data from phase 1 trial(s) and initiate development of efficacy trial(s), if appropriate.	(FY06) Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.
SRO-3.2	Target adjusted due to scientific insight on developing lead compounds.	(FY05) Develop a lead compound for one of the molecules or mechanisms identified as a potential target for broad spectrum antimicrobial drug development.	(FY05) Develop a set of screening tools that will help evaluate potential compounds/classes of compounds for activity against multiple bacterial and viral infections.
SRO-4.2	Target adjusted due to	(FY04) Determine if slowing the metabolism	(FY04) Conduct dose response studies of

	scientific insight on rotenone/inhibitor interactions.	of rotenone through the cytochrome P-450 inhibition facilitates creation of a mouse model of PD.	chronic rotenone administration in normal mice and assess resulting changes in striatal dopamine levels and the number of dopamine neurons in substantia nigra.
SRO-8.5	New goal representative of reporting on Roadmap		By 2009, develop a centralized reporting system to improve the assessment of non-specific symptoms (i.e., pain and fatigue) and other health-related quality of life measures.

For the non-scientific functional areas, both targets and goals were changed to better reflect current NIH administrative and management policies. Several goals were reworded to improve ongoing monitoring, updating, and reporting. This enhancement will enable longitudinal reporting of management data. The changes are summarized in the table below.

GOAL IDENTIFIER	DESCRIPTION OF CHANGE	PREVIOUS WORDING	NEW WORDING
CTR-4	Targets revised	(FY04) Implement the trans-NIH Commercialization Assistance Program (CAP) based on the recent CAP pilot.	Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization. (FY04) CAP (FY05) Niche Assessment
		(FY04) Initiate pilots for additional programs of technical assistance services.	(FY04, 05) Implement effective piloted programs to create a menu of technical assistance programs.
		(FY05) Achieve higher than baseline indication of progress toward solution of technical problems or commercialization for participants in CAP pilot.	(FY04, 05) Report critical elements to assess advances of each technical assistance program.
		(FY05) Increase by 5 percent the SBIR awardees who successfully identify appropriate resources and partners through the programs of technical assistance services.	
CBRR-1	Targets revised	(FY04) Achieve 100% of the asymptotic targets for the number of K23, and K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research.	Achieve 100% of the asymptotic targets for the number of K23, and K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research. 120 K23 FY04-FY06 50 K24 FY04-FY06 50 K30* FY04-FY06
	Baseline changed	(FY03) 120 K23 awards for FY03-FY06 50 K24 awards for FY03-FY06 50 K30* awards for FY03-FY06	(FY99-FY02) Awards granted K23 645 K24 263 K30 59
		(FY03) NRSA Group: 7,125 Comparison Group A: 9,985 Comparison Group B: 9,229	Award rates NRSA Group: 46% Comparison Group A: 35% Comparison Group B: 26%
CBRR-2	Target revised	(FY03) Deploy the general ledger/budgeting module.	Deploy the general ledger/budgeting module. FY03 Program steps a-i
		(FY03) Deploy the travel module.	Deploy the travel module. FY03 Program steps a-i

GOAL	DESCRIPTION OF CHANGE	PREVIOUS WORDING	NEW WORDING
		(FY04) Deploy the property and contracts/ acquisition/ accounts payable and receivable/ supply modules.	Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' FY06 Program steps h-I 'Final review'
		(FY04) Deploy the service and supply fund activities module.	Deploy the service and supply fund activities module. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' FY06 Program steps h-I 'Final review'
CBRR-3	Target revised	(FY04) Implement a core hospital system, including scheduling and resource utilization modules and pharmacy management system.	(FY04) Implement a core hospital system.
CBRR-4	Goal revised	Provide greater functionality and more streamlined processes in grants administration by continuing to develop NIH electronic research administration (eRA).	Provide greater functionality and more streamlined processes in grants administration by developing and monitoring the NIH electronic research administration (eRA). (ongoing)
	Targets added		(FY04) Develop plan to integrate OPDIVs (FY05) Initiate OPDIV integration (FY05) Continue conversion of Business Processes; 25% of business processes being done electronically
SMHC-1	Goal achieved and therefore dropped.		
SMHC-2	Goal combined with SMHC-3	Identify and develop potential successors for critical leadership positions by (1) developing and implementing an NIH-wide succession planning process that assesses the gaps between senior leadership needs and talent available; (2) identifying leadership competencies that will be critical to the mission of NIH now and in the future; and (3) providing developmental opportunities that will prepare potential successors to meet the demands required of senior leadership positions.	Improve the strategic management of NIH human resources by developing and monitoring a comprehensive human capital plan based on the Agency's programmatic objectives and projected future needs. (ongoing)
SMHC-3	Goal incorporated SMHC-2 and existing targets revised	(FY04) Considering the scientific agenda, applicable DHHS management initiatives, and future workforce trends, project the NIH human capital needs for the next 3 to 5 years.	(FY04) Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.
		(FY04) Using the standards for success outlined in Office of Personnel Management's Human Capital Assessment and Accountability Framework (i.e., the Framework), assess where NIH strengths and weaknesses exist regarding management of human capital.	(FY04) Conduct a study to identify competencies needed by NIH leaders who will drive future development efforts.
		(FY05) Implement succession planning and leadership development processes for critical positions.	(FY05) Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.
		(FY05) Revise the NIH Strategic workforce plan to include new projections regarding human capital requirements and expand it to include an associated system of human capital management accountability.	(FY05) Establish performance indicators with baselines related to recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.
SMHC-4	Target revised	(FY 05) Implement transition services for employees annually displaced due to prior year's competitive sourcing.	(FY05) Evaluate transition services provided to employees.

GOAL IDENTIFIER	DESCRIPTION OF CHANGE	PREVIOUS WORDING	NEW WORDING
SMHC-5	New goal		Improve and monitor the use of human resource services by providing real-time access to tools via the NIH Portal. (Ongoing)
	FY05 targets		(FY05) Develop an HR Community on the NIH Portal to become the primary site for NIH HR information, systems and resources. (FY05) Identify HR critical elements and tools to monitor use and quality of the HR information.
POI-1	Goal revised	Ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing an Earned Value Analysis and Management System (EVAMS).	Ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing and monitoring an Earned Value Analysis and Management System (EVAMS). (ongoing)
	Targets revised	(FY04) Evaluate and assess existing project management systems and implement them into a proof-of-concept version of the NIH EVAMS.	(FY04) Evaluate and assess existing project management systems integrating findings for implementation of a proof-of-concept version of NIH's Earned Value Management System (EVMS).
		(FY05) Implement a revised project management system that incorporates earned value analysis and management	(FY05) Implement a revised project management system that incorporates Earned Value Analysis and Management principles to evaluate on time and within budget delivery of projects.
POI-2	Goal revised	Expand the use of Performance-Based Contracting (PBC).	Utilize Performance-Based Contracting (PBC). (ongoing)
	Target revised	(FY05) Obligate 50% of eligible service contracting dollars through PBC.	(FY05) Obligate 40% of eligible service contracting dollars through PBC.
POI-3	Goal achieved and therefore dropped		
POI-4	Target revised	(FY05) Implement recommendations from the internal compliance reviews held in 2004.	(FY05) Implement recommendations from the internal compliance reviews held in 2004. By the end of FY 2005 NIH will have developed an ongoing program for internal compliance reviews which, combined with other continuing efforts, will complete the goal of developing a strong program to ensure proper stewardship of public funding for research.

LINKS TO HHS AND AGENCY STRATEGIC PLANS

NIH GPRA PERFORMANCE GOALS and TARGETS	Associated DHHS Strategic Plan Objective	Associated "One HHS" Management Objective / Program	Associated Healthy People 2010 Focus Area	Associated PMA Initiative
Scientific Research Outcomes (SRO)				
Goal 1.1) By 2005, conduct medications development using animal models and begin conducting Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin.	1.4: Reduce Substance Abuse. 4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objective 7	26: Substance Abuse	NA
Goal 1.2) By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability. 6.2: Increase the proportion of older Americans who stay healthy and active.	Program Objective 7	28: Vision and Hearing	NA
Goal 2.2) By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objective 7	19: Nutrition and Overweight	NA
Goal 2.3) By 2006, develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objective 7	NA	NA
Goal 3.1) By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD).	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability. 6.2: Increase the proportion of older Americans who stay active and healthy.	Program Objectives 7, 9	18: Mental Health and Mental Disorders	NA
Goal 3.2) By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.	2.1: Build the capacity of the health care system to respond to public health threats in a more timely manner, especially bioterrorism threats. 4.1: Advance the understanding of basic biomedical and behavioral science and	Program Objectives 3, 4, 7	14: Immunization and Infectious Diseases 24: Respiratory Diseases	NA

NIH GPRA PERFORMANCE GOALS and TARGETS	Associated DHHS Strategic Plan Objective	Associated "One HHS" Management Objective / Program	Associated Healthy People 2010 Focus Area	Associated PMA Initiative
	how to prevent, diagnose, and treat disease and disability.			
Goal 3.3) By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objective 7	NA	NA
Goal 3.4) By 2010, develop an HIV/AIDS vaccine.	1.2: Reduce the incidence of sexually transmitted diseases and unintended pregnancies. 4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objectives 3, 4, 7	13: HIV	NA
Goal 3.2.1) By 2007, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objective 7	5: Diabetes	NA
Goal 4.1) By 2004, develop two new animal models to use in research on at least one agent of bioterror.	2.1: Build the capacity of the health care system to respond to public health threats in a more timely manner, especially bioterrorism threats. 4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objectives 4, 7	14: Immunization and Infectious Diseases	NA
Goal 4.2) By 2005, develop improved animal models that best recapitulate Parkinson's disease (PD) based on emerging scientific findings of genetic or environmental influences or interactions of genes and the environment on the development of PD.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objectives 7, 9	8: Environmental Health	NA

NIH GPRA PERFORMANCE GOALS and TARGETS	Associated DHHS Strategic Plan Objective	Associated "One HHS" Management Objective / Program	Associated Healthy People 2010 Focus Area	Associated PMA Initiative
Goal 5.1) By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than current recommended HIV treatment regimens.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objective 7	13: HIV	NA
Goal 5.2) By 2009, determine the efficacy of statins in preventing the progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objective 7	12: Heart Disease and Stroke	NA
Goal 5.3) By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objective 7	NA	NA
Goal 5.4) By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objectives 3, 5, 7	18: Mental Health and Mental Disorders 26: Substance Abuse	NA
Goal 5.5) By 2008, develop and test new evidence-based treatment approaches for drug abuse in community settings.	1.4: Reduce substance abuse. 3.4: Eliminate racial and ethnic health disparities.	Program Objectives 5, 7	26: Substance Abuse 27: Tobacco Use	NA
Goal 6.1) By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability. 6.2: Increase the proportion of older Americans who stay active and healthy.	Program Objectives 7, 9	28: Vision and Hearing	NA
Goal 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.	1.1: Reduce behavioral and other factors that contribute to the development of chronic diseases. 4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objectives 7, 9	4: Chronic Kidney Disease 5: Diabetes 12: Heart Disease and Stroke	NA

NIH GPRA PERFORMANCE GOALS and TARGETS	Associated DHHS Strategic Plan Objective	Associated "One HHS" Management Objective / Program	Associated Healthy People 2010 Focus Area	Associated PMA Initiative
Goal 6.3) By 2012, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objectives 6, 7	8: Environmental Health	NA
Goal 7.1) By 2005, evaluate 10 commonly used botanicals for inhibition/induction of enzymes that metabolize drugs as a method of identifying potential botanical-drug interactions.	5.1: Reduce medical errors. 2.2: Improve the safety of food, drugs, biological products, and medical devices. 4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objectives 4, 6, 7	NA	NA
Goal 7.2) By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability. 4.2: Accelerate private sector development of new drugs, biologic therapies, and medical technology.	Program Objectives 6, 7, 9	3: Cancer	NA
Goal 7.3) By 2005, create the next-generation map of the human genome, a so-called haplotype map ("HapMap"), by identifying the patterns of genetic variation across all human chromosomes.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objectives 6, 7	NA	NA
Goal 8.1) By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases.	1.2: Reduce the incidence of sexually transmitted diseases and unintended pregnancies. 2.1: Build the capacity of the health care system to respond to public health threats in a more timely manner, especially bioterrorism threats. 4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objectives 3, 4, 7	10: Food Safety 14: Immunization and Infectious Diseases 24: Respiratory Disease 25: Sexually Transmitted Diseases	NA

NIH GPRA PERFORMANCE GOALS and TARGETS	Associated DHHS Strategic Plan Objective	Associated "One HHS" Management Objective / Program	Associated Healthy People 2010 Focus Area	Associated PMA Initiative
Goal 8.2) By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability. 6.2: Increase the proportion of older Americans who stay active and healthy.	Program Objectives 7, 9	2: Arthritis, Osteoporosis, and Chronic Back Conditions	NA
Goal 8.3) By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, nonredundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA) transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objective 7	NA	NA
Goal 8.4) By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding.	4.3: Strengthen and diversify the pool of qualified health and behavioral science researchers.	Program Objective 7	23: Public Health Infrastructure	NA
Goal 8.5) By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease.	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability.	Program Objectives 5, 7	NA	4: Expanded Electronic Government
Goal 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).	4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability. 6.2: Increase the proportion of older Americans who stay active and healthy.	Program Objectives 3,7	5: Diabetes 12: Heart Disease and Stroke 18: Mental Health and Mental Disorders	NA

NIH GPRA PERFORMANCE GOALS and TARGETS	Associated DHHS Strategic Plan Objective	Associated "One HHS" Management Objective / Program	Associated Healthy People 2010 Focus Area	Associated PMA Initiative
Goal 9.2) By 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities.	1.1: Reduce behavioral and other factors that contribute to the development of chronic diseases. 3.4: Eliminate racial and ethnic health disparities. 4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability. 4.4: Improve the coordination, communication, and application of health research results.	Program Objectives 1, 3, 7	7: Educational and Community-Based Programs 12: Heart Disease and Stroke	NA
Communication and Transfer of Results (CTR)				
Goal 1) By 2008, reduce the disparity between African American and white infants in back sleeping by 50% to further reduce the risk of sudden infant death syndrome (SIDS).	3.4: Eliminate racial and ethnic health disparities.	Program Objectives 1, 6	11: Health Communication 16: Maternal, Infant, and Child Health	NA
Goal 2) By 2006, increase awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least five communities and extending the impact of the National Institute of Neurological Disorders and Stroke campaign "Know Stroke. Know the Signs. Act in Time."	1.1: Reduce behavioral and other factors that contribute to the development of chronic diseases. 4.4: Improve the coordination, communication, and application of health research results.	Program Objectives 3, 6	11: Health Communication 12: Heart Disease and Stroke	NA
Goal 3) Through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.	4.4: Improve the coordination, communication, and application of health research results.	NA	NA	NA
Goal 4) Increase the percentage of Small Business Innovation Research (SBIR) Program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.	4.2: Accelerate private sector development of new drugs, biologic therapies, and medical technology. 4.4: Improve the coordination, communication, and application of health research results.	Program Objective 6	NA	NA
Capacity Building and Research Resources (CBRR)				
Goal 1) Recruit, train, and retain a diverse population of highly trained scientists in biomedical, behavioral, and clinical research using research training grants, fellowships, career development awards, and student loan repayment programs.	4.3: Strengthen and diversify the pool of qualified health and behavioral science researchers.	Management Objective 2 Program Objective 7	23: Public Health Infrastructure	NA

NIH GPRA PERFORMANCE GOALS and TARGETS	Associated DHHS Strategic Plan Objective	Associated "One HHS" Management Objective / Program	Associated Healthy People 2010 Focus Area	Associated PMA Initiative
Goal 2) Promote data sharing and provide information in real time by implementing the NIH Business System.	8.4: Improve financial management. 8.5: Enhance the use of information technology in service delivery and record keeping.	Management Objective 2 Program Objective 5	NA	3: Improved Financial Performance
Goal 3) Streamline business processes and automate data movement by implementing the Clinical Research Information System (CRIS).	5.1: Reduce medical errors. 5.2: Increase the appropriate use of effective health care services by medical providers. 5.5: Accelerate the development and use of an electronic health information infrastructure. 8.5: Enhance the use of information technology in service delivery and record keeping.	Management Objective 2 Program Objective 5	NA	3: Improved Financial Performance 4: Expanded Electronic Government
Goal 4) Provide greater functionality and more streamlined processes in grants administration by continuing to develop the NIH electronic research administration (eRA).	8.5: Enhance the use of information technology in service delivery and record keeping.	Management Objective 2 Program Objective 5	NA	4: Expanded Electronic Government
Strategic Management of Human Capital (SMHC)				
Goal 2) Identify and develop potential successors for critical leadership positions by (1) developing and implementing an NIH-wide succession planning process that assesses the gaps between senior leadership needs and talent available; (2) identifying leadership competencies that will be critical to the mission of NIH now and in the future; and (3) providing developmental opportunities that will prepare potential successors to meet the demands required of senior leadership positions.	8.2: Improve the strategic management of human capital.	Management Objective 2	23: Public Health Infrastructure	1: Strategic Management of Human Capital
Goal 3) Improve the strategic management of NIH resources by developing a comprehensive human capital plan based on the Agency's programmatic objectives and projected future needs.	8.2: Improve the strategic management of human capital.	Management Objective 2	23: Public Health Infrastructure	1: Strategic Management of Human Capital
Goal 4) Ensure that NIH commercial functions are performed as efficiently and cost-effectively as possible by conducting competitive sourcing reviews on the required number of functions within the Agency's commercial inventory.	8.3: Enhance the efficiency and effectiveness of competitive sourcing. 8.4: Improve financial management.	NA	NA	2: Competitive Sourcing 3: Improved Financial Performance

NIH GPRA PERFORMANCE GOALS and TARGETS	Associated DHHS Strategic Plan Objective	Associated "One HHS" Management Objective / Program Objective	Associated Healthy People 2010 Focus Area	Associated PMA Initiative
Goal 5) Improve and monitor the use of human resource services by providing real-time access to tools via the NIH Portal.	8.5: Enhance the use of information technology in service delivery and record keeping.	Management Objective 2	NA	4: Expanded Electronic Government
Program Oversight and Improvement (POI)				
Goal 1) Ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing an Earned Value Analysis and Management System (EVAMS).	8.5: Enhance the use of information technology in service delivery and record keeping.	Management Objective 2	NA	5: Budget and Performance Integration
Goal 2) Expand the use of Performance-Based Contracting (PBC).	8.4: Improve financial management.	NA	NA	1: Strategic Management of Human Capital 5: Budget and Performance Integration
Goal 3) Improve accountability for organizational performance results and support for the President's Management Agenda by linking employee performance management plans/contracts to NIH program and management priorities.	8.1: Create a unified HHS committed to functioning as one Department. 8.2: Improve the strategic management of human capital. 8.4: Improve financial management. 8.6: Achieve integration of budget and performance.	Management Objective 1	NA	1: Strategic Management of Human Capital 5: Budget and Performance Integration
Goal 4) Ensure proper stewardship of public funding for research.	8.2: Improve the strategic management of human capital. 8.4: Improve financial management. 8.6: Achieve integration of budget and performance.	Program Objective 7 Management Objective 10	NA	5: Budget and Performance Integration

PARTNERSHIPS AND COORDINATION

The NIH activities complement the efforts of sister DHHS agencies in many ways, and NIH actively coordinates across DHHS agencies. Many initiatives are undertaken in partnership with other DHHS agencies. These partnerships and coordinations provide evidence that the agencies are working together to eliminate duplication and overlap.

Correlation and Coordination

As a research agency, NIH's relationship with sister DHHS agencies is bidirectional; that is, NIH both receives information from and contributes information to other operating divisions/agencies (OPDIVs). Information collected by other DHHS agencies helps to inform NIH priority-setting processes in important ways. For example, the extensive data on disease prevalence and incidence collected by the Centers for Disease Control and Prevention (CDC) is a key source of knowledge about the burden of illness. In turn, NIH is often an important source of expertise for sister agencies. For example, prior to issuing regulations, the Food and Drug Administration (FDA) often seeks comment from NIH. Below are examples of trans-DHHS single and multi-agency collaborations.

Trans-DHHS Single Collaborations

NIH institutes and centers collaborate with other DHHS agencies to efficiently maximize resources and expertise, advance scientific discoveries, and translate these discoveries into policies and programs that benefit the Nation. Just a few examples of these numerous efforts are described below

Selected Collaborations with Center for Disease Control and Prevention (CDC)

- In November 2003, the *U.S. Cancer Statistics: 2000 Incidence* was released. This is the most comprehensive federal report available on state-specific cancer incidence rates. This report was a collaboration among the CDC, and the National Cancer Institute (NCI) and the North American Association of Central Cancer Registries. These organizations combined their data to produce the official federal statistics on cancer incidence. Having a single source of information minimizes overlapping activities and duplication of efforts.[111]

- The National Institute of Environmental Health Sciences (NIEHS) and the CDC jointly funded research for a study in mice, of how a black mold, or fungus, causes infant lungs to hemorrhage, often killing them. The spore of this fungus *(Stachybotrys atra)* contains very potent mycotoxins-toxin produced by fungi that appear to be particularly toxic to the rapidly growing lungs of young infants.[121]

Selected Collaboration with the Administration on Aging (AoA)

- The Administration on Aging (AoA) joined the National Institute of Mental Health (NIMH) in the wide-spread dissemination of the fact sheet "Older Adults: Depression and Suicide Facts." The fact sheet focuses on recognizing signs of depression, reducing suicide risk in older adults, and promoting treatment. AoA and NIMH made the information available nationwide on this widely under recognized and under treated illness.[131]

Selected Collaboration with the Substance Abuse and Mental Health Services Administration (SAMHSA)

- National Institute on Drug Abuse (NIDA) research and SAMHSA physician training combined to put care for opiate dependence in the hands of family doctors. Buprenorphine, a new medication developed by the NIDA will now be available to treat heroin and other opioid dependence through the certification and training of physicians to use the medication. Buprenorphine will allow patients to be treated for addictions in the same manner as they are treated for other chronic illnesses, such as diabetes and hypertension.[141]

Selected Collaborations with the Federal Food and Drug Administration (FDA)

- The National Institute of Biomedical Imaging and Bioengineering (NIBIB) at the NIH and the Center for Devices and Radiological Health (CDRH) at the FDA signed an interagency agreement to establish a joint Laboratory for the Assessment of Medical Imaging Systems. The purpose of this joint venture is to assess and optimize high-resolution, high dimensional medical imaging systems. The joint agreement will provide an avenue for exploring innovative and high-quality technologies and interdisciplinary research that will lead to improved healthcare.[151]

- The NCI and the FDA announced two collaborative initiatives to facilitate the development and use of better cancer treatments. The new initiatives are to:
  - Link cancer researchers around the U.S. electronically to the FDA, thereby reducing the time it takes for promising new drugs to be reviewed for testing in clinical trials, and
  - Initiate Cancer Fellowship Training Programs aimed at developing corps of physicians and scientists, expert in clinical research, the regulatory approval process and translation of research breakthroughs to clinical practice.[161]

- The NIH and the FDA launched a new Genetic Modification Clinical Research Information System (GeMCRIS) - a Web-accessible database on human gene transfer. GeMCRIS, developed collaboratively by the two agencies, is a unique public information resource as well as an important new electronic tool to facilitate the reporting and analysis of adverse events on these trials. The new system will provide information to the public directly and will improve the government's ability to monitor adverse events in gene transfer research, also known as gene therapy.[171]

Multi-Agency Collaborations

- CRISP (Computer Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions. The database, maintained by the Office of Extramural Research (OER) at the NIH, includes projects funded by the NIH, SAMHSA, HRSA, FDA, CDC, AHRQ, and Office of Assistant Secretary of Health (OASH). Users, including the public, can use CRISP interface to search for scientific concepts, emerging trends and techniques, or identify specific projects and/or investigators.[181]

- The NIH Office of Medical Applications of Research (OMAR) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Child Health and Human Development (NICHD), the FDA, the National Institute of Standards and Technology (NIST) and the NIH Office of Research on Women's Health formed a cooperative panel charged with reviewing all of the available evidence on total knee replacement (TKR). The panel found that for persons suffering from intractable and persistent knee pain and disability, TKR surgery is a safe and cost effective therapy that restores mobility and alleviates discomfort. The panel also reported that there is clear evidence of racial, ethnic and gender disparities in the provision of TKR, as there is for many other health care interventions, but the reasons for this were unclear.[191]

- The Aberdeen Area Infant Mortality Study was funded by three agencies of the Department of Health and Human Services: the Indian Health Service (IHS), the NICHD, and the CDC. The study identified important risk and protective factors for Sudden Infant Death Syndrome (SIDS) among this group of American Indians. This strengthened public health nurse visiting programs and programs to reduce alcohol consumption among women of childbearing age potentially aiding in the reduction of the high incidence of SIDS. Nine tribes and one urban American Indian community participated in the study.[1101]

- The HIV/AIDS Treatment Adherence Health Outcomes and Cost Study was the first Federal effort to focus on people living with HIV/AIDS who have also been diagnosed with mental and addictive disorders. This study represents collaboration among SAMHSA, HRSA, and several Agencies of NIH. The DHHS Goal of this multi-site study was to determine the effects of integrated mental

health, substance abuse, health outcomes and costs. Preliminary findings suggest that the participants were more likely to have received HIV/AIDS and substance abuse treatment than mental health services.[1111]

The NIMH, NIDA, and National Center on Minority Health and Health Disparities (NCMHD), joined with the SAMHSA, CDC and other agencies to systematically examine the Psychiatric Disorders Common Among Detained Youth. Conducted in the Chicago area, the new study was the largest and most methodologically sophisticated of its kind. Among teens in Juvenile detention, nearly two thirds of boys and nearly three quarters of girls have at least one psychiatric disorder. These rates dwarf the estimated 15 percent of the youth in the general population thought to have psychiatric illness.[1121]

The NCI, CDC, and the Agency for Healthcare Research and Quality all are working on the DHHS Goal on reducing tobacco use. NCI has a web site at www.smokefree.gov that provides guidance to state and national resources for helping smokers quit. NCI and other HHS agencies provide expert assistance to the Federal Trade Commission in determining whether claims of reduced risk in tobacco product are deceptive, i.e., false, misleading, or not adequately supported by scientific evidence.[1131]

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[121] National Institutes of Health, NIEHS Press Release. NIEHS, CDC Fund Study of Fungus Fatal to Cleveland Infants. July 1997. http://www.niehs.nih.gov/oc/news/mold.html p.1-2.
[131] National Institutes of Health, Press Release National Institute of Mental Health, Educating Older Americans and Health Professionals about the Risk of Depression. August 1, 1999. http://www.nimh.nih.gov/eventrs/prolderadults.cfm. P.1.
[141] National Institutes of Health, News Advisory. NIDA Research and SAMHSA Physician Training Combined to Put Care for Opiate Dependence in the Hands of Family Doctors. October 9, 2002. http://www.nih.gov/new2s/pr/oct2002/nida-09.htm p.1
[151] National Institutes of Health, NIH News. NIBIB and CDRH Sign Interagency Agreement Establishing Joint Laboratory. February 17, 2004. http://www.nih.gov/news/pr/feb2004/nibib-17.htm p.1
[161] National Institutes of Health, NIH News. NCI, FDA Announce Two New Initiatives as Part of Strategic Partnership. November 12, 2003. http://www.nih.gov/news/pr/nov2003/nci-12.htm p.1
[171] National Institutes of Health, NIH News. NIH and FDA Launch New Human Gene Transfer Research Data System. March 26, 2004, p.1
[181] National Institutes of Health, Office of Extramural Research. Computer Retrieval of Information on Scientific Projects CRISP - A Database of Biomedical Research. March 8, 2004. http://crisp.cit.nih.gov/ p.1.
[191] National Institutes of Health, NIH News. NIH Consensus Panel Confirms Effectiveness of Total Knee Replacement. December 10, 2003. http://www.nih.gov/news/pr/dec2003/od-10a.htm p.1.
[1101] National Institutes of Health, Press Release. Study Identifies SIDS Risk Factors Among American Indian Infants. December 2, 2002. http://www.nih.gov/news/pr/dec2002/nichd-03.htm p.1.
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[1121] National Institutes of Health, NIH News Release. Psychiatric Disorders Common Among Detained Youth. December 9, 2002. http://www.nih.gov/news/pr/dec2002/nimh-09.htm p.1
[1131] U.S Department of Health and Human Services. Program Review - Tobacco Use. May 2003. http://www.healthypeople.gov/data/2010prog/focus27/default.htm pp.1-2

DATA VERIFICATION AND VALIDATION

Types of Data Sources

Data for Quantitative and Other Goals with Definitive End Points

Most of NIH's performance goals contain quantitative or otherwise objective targets. The data for assessing objective/quantitative performance goals come from a variety of NIH sources:

- **Completion of Studies/Actions**—Where a goal is to complete an action (e.g., respond to a recommendation), documenting evidence is provided that confirms the completion or status of the action. Studies and reports developed by and for the use of peer review and advisory councils and other distinguished independent panels and committees are examples of the information useful for this type of GPRA reporting.

- **Program Evaluation**—Objective evaluation studies and analyses are already a well-established component of NIH's regular planning and management activities for its programs. Such studies are used to provide basic data on program performance, identify avenues for program improvement, and consider the implications of emerging issues on program operation. NIH also conducts various special evaluation studies in association with such agencies as the National Academy of Sciences and the National Science Foundation - such as large-scale, long-term studies of scientific personnel and training needs, research facilities, and research instrumentation.

- **Data Tracking and Collection Systems**—Most performance comparisons for quantitative goals are based on data from information systems that are designed to track a particular operation. NIH has established and maintains a number of large-scale databases to meet its ongoing management needs (such as IMPAC - see below) or with other Federal agencies (such as Interagency Edison, see below). These databases play a role in the agency's GPRA performance assessment process. In general, these are public databases, created over a number of years through competitive proposals and subject to outside review by knowledgeable experts, and are maintained through standard database quality protocols. These data are widely regarded, within and outside of NIH, as providing a credible picture of various aspects of the Nation's biomedical research enterprise.

The table below identifies some of the data systems that are currently used at NIH to track and develop data for performance comparisons.

SYSTEM	PURPOSE	TYPES OF DATA
IMPAC (Information for Management, Planning, Analysis, and Coordination)	IMPAC is a comprehensive database system covering NIH's extramural research activities.	• Records of research contracts • Records of in-process grant applications • Interagency and intra-agency agreements
DCIS (Departmental Contracts Information System)	DCIS provides data collection and reporting capabilities needed to enable DHHS to comply with the reporting requirements mandated by Public Law 93-400.	• Contract actions for awards with an anticipated award value over $25,000
CMMS (Computerized Maintenance Management System) PIN (Project Information Network)	Together, these systems are used to manage and monitor the acquisition, design, construction, modernization, replacement, and/or enhancement of NIH's capital assets.	• Acquisition strategy • Project status • Proposed schedules • Actual schedules • Proposed costs • Actual costs • Management reports
WWW (World Wide Web)	Use of the WWW allows worldwide sharing of data, information, images, and sound to be posted and transmitted electronically.	• Genomic sequences • NIH policy and procedure documents • Clinical trial databases • Reports on use of Web sites

Data for Descriptive Goals
The "Alternative Form" assessment approach used for many of NIH's scientific research outcome goals poses some unique issues for data validation and verification. Nonetheless, virtually all of the outside advisory groups that have looked at this issue over the past several years (e.g., the White House Office of Science and Technology Policy, NAS panels and committees, the Office of Naval Research, and various other science agencies) have affirmed the centrality of peer review by technical experts in preparing findings about the productivity of basic research programs. (See, for example, the 1999 and 2001 NAS reports *Evaluating Federal Research Programs: Research and the Government Performance and Results Act* [19991 and *Implementing the Government Performance and Results Act for Research* [20011.)

The approach NIH uses to prepare these annual assessments of its research goals relies chiefly on such a peer review process. The most prominent sources of data are science advances validated through the verification process inherent in the course of publication.

GOAL-BY-GOAL VERIFICATION AND VALIDATION

Scientific Research Outcomes
Performance on the targets for each Scientific Research Outcome goal is verified through citation of appropriate documentation. For example, verification and validation of performance on progress targets might include:

- Notices for solicitations of research applications e.g., RFAs, RFPs, PAs, and PARs, including date the solicitation was published on http://www.grants.gov
- Cooperative Research and Development Agreements
- Initiated or active clinical trials, including citation of the extramural award(s) and intramural projects
- Workshops, meetings, and conferences that could be validated by copies of agendas, proceedings, reports, or other program records
- Working groups, coordinating committees, or advisory groups that could be validated by copies of rosters, meeting agendas, minutes, and other program records
- Strategic plans and research agendas validated by citations of the documents

Verification and validation of performance on output and outcome targets might include:

- Peer-reviewed journal articles (citations including publication journal and date and/or URL)
- Annual progress reports from grants/contracts
- Reports from databases maintained by clinical trial statistical centers
- Electronic databases or resources for information (URLs)
- Patents
- Licenses

FY 2004 actual verifications

GOAL	SOURCE VALIDATION
SRO 1.1	"Antalarmin preclinical toxicology summary; prepared by Toxicology and Pharmacology Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, NCI, May 2004" (contact: NIAAA, Karen Peterson) Broadbear, JH, Winger G, Rivier JE, Rice KC, Woods JH. "Corticotropin-releasing hormone antagonists, Astressin B and Antalarmin: Differieng profiles of activity in Rhesus Monkeys." Neuropsychopharmacology (2004) 29: 1112-1121. Eric P Zorrilla & George F Koob. "The therapeutic potential of CRF1 antagonists for anxiety" Expert Opin. Investig. Drugs (2004) 13(7):799-828 www.clinicaltrials.gov (search term: rimonabant)

SRO 1.2	Patents approved and filed based upon work done for this project 1) Ronald Miles, Sanjay Sundermurthy, Colum Gibbons, Ronald Hoy, and Daniel Robert, United States Patent #6,788,796 B1 (2004), "Differential Microphone." This invention describes a novel differential microphone diaphragm that has improved frequency response, increased sensitivity, and lower noise over existing approaches. Differential microphones form the basis of any pressure sensing microphone that has a response that depends on the direction of the sensed sound. Current differential microphones are designed so that the difference in the sound at two points in space results in a net force on a simple flat diaphragm. The resulting deflection of the diaphragm is proportional to the pressure difference. In this invention, differences in pressure at two points in space produce a net moment, or torque on the diaphragm causing it to rock, or tilt, in response to differences in pressure. 2) R. Miles and W. Cui, "Robust Diaphragm for an Acoustic Device,", filed 10/20/2003. This invention consists of a microphone diaphragm that can be made out of silicon or any similar material used in microfabrication. The microphone diaphragm maintains exceptional flatness under the influence of either compressive or tensile stresses that may arise during fabrication. The dynamic response of the diaphragm is extremely close to that of an ideal flat plate over a frequency range extending well beyond the audible range. The dynamic characteristics may be readily tuned without adversely influencing the flatness or ruggedness of the device. The design concept is highly robust and is tolerant of a number of fabrication defects. 3) F.L. Degertekin, N.A. Hall and W. Lee, "Highly-sensitive displacement-measuring optical device," U.S. Patent application, filed 11/10/2003. The invention discloses several embodiments of an optical sensor based on microscale phase sensitive diffraction grating. The sensor measures the displacement of a reflector in a sensitive manner as well as any changes in the optical properties of the reflector or the sensor structure due to external physical or chemical stimuli. The applications of the sensor include, but not limited to, microphones, pressure sensors, chemical sensors, and arrays of these sensors built in a very small volume. 4) A.S. Feng, M.E. Lockwood, D.L. Jones, R.C. Bilger, W.D. O'Brien, and B.C. Wheeler, "System and Methods for Interference Suppression with Directional Sensing Patterns,"{\it Assignee: Board of Trustees of the University of Illinois},U.S. Patent application filed April 9, 2003. Abstracts Presented at Meetings Wu, N. Eva (Binghamton Univ.), Miles, Ronald (Binghamton Univ.), Aydin, Oguz (Binghamton Univ.) A Digital Feedback Damping Scheme for a Micromachined Directional Microphone 2004 American Control Conference, June 30 - July 2, 2004, Boston, Massachusetts, USA In this paper, a method for introducing active damping for a diaphragm in a micromachined directional microphone is considered. The sigma-delta modulation is used to circumvent the nonlinearity of the capacitive transducers of the microphone. The principle of operation of the damping scheme is explained, and the simulation results of a lumped diaphragm model are presented. C. Schmitz, C., N. Iyer, M.E. Lockwood, C.R. Lansing, and D.L. Jones, "Enhanced BTE Directivity Using a Directional Microphone Array," IHCON 2004: International Hearing Aid Research Conference}, Tahoe City, CA, August 25--29, 2004. ***Journal Publications*** D. Jones, M.E. Lockwood, C.R. Lansing, and A.S. Feng, "Improved BTE hearing aid directivity using a directional microphone array," Journal of the Acoustical Society of America}, vol. 115, no. 5, Pt. 2, May 2004, p. 2598. Wook Lee, Neal Hall, and F. Levent Degertekin, "A grating-assisted resonant-cavity-enhanced optical displacement detection method for micromachined sensors," Applied Physics Letters, vol. 85, no. 15, October 11, 2004, p. 3032-3034. Wook Lee and F. Levent Degertekin, "Rigourous Coupled-Wave Analysis of Multiulayered Grating Structures," IEEE Journal of Lightwave Technology, vol 22, no. 10, October 2004, p. 2359-2363. ***Accepted for publication*** Dorel Homentcovschi and Ron Miles, "Modelling of viscous damping of perforated planar microstructures. Applications in acoustics," Journal of the Acoustical Society. R.N. Miles and D. Homentcovschi, "Viscous Damping of Perforated Micromechanical Structure," Sensors and Actuators.
SRO 2.2	Search http://crisp.cit.nih.gov/ for the following grant numbers: • 1R01HL079491-01

	• 1R01HL079511-01 • 1R01HL079478-01 • 1R01HL079546-01 • 1R01HL079483-01 • 1R01HL079505-01 • 1R01HL079509-01 The NICHD/NIH orlistat study: McDuffie JR et al. J Ped Endocrinol Metab 17(3):307-19, 2004. The urls for the initiative entitled "Transdisciplinary Research on Energetics and Cancer" are: • http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-010.html • http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-011.html
SRO 2.3	The conserved Domain database is publicly available via the PubMed / Entrez search engine: http://www.ncbi.nlm.nih.gov/gquery/gquery.fcgi. Sequence similarity searches are also supported via the available CD-Search utility: http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi
SRO 3.1	A copy of the awarded contract (Investigational New Drug Toxicology for Drugs to Treat AD and Other Aging Related Dementias - AG4-0010) is available in the NIH/OD/OA/ Office of Logistics and Acquisition Operations (OLAO)/Division of Research Acquisitions; 6100 Executive Boulevard, Room 6E01, Bethesda, MD 20892; tel 301-496-4487 (Contact is Valerie Pickett) 3rd Intervention Testing Program award - search http://crisp.cit.nih.gov/ for the following grant number: 1U01AG022307-01 Information on the ITP: http://www.nia.nih.gov/ResearchInformation/ScientificResources/InterventionsTestingProgram.htm
	RFA entitled "Collaborative Studies on Alzheimer and Related Diseases" at: http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-05-006.html ADNI $60 million initiative - search http://crisp.cit.nih.gov/ for the following grant number: 1U01AG024904-01 PIB compound - Klunk WE, Engler H, Nordberg A, et al.: Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 55:306-319, 2004. APOE s4 - Reimen EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J: Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. Proc Natl Acad Sci 101(1):284-289, 2004. Recruitment for siblings and genetics study - http://clinicaltrials.gov/show/NCT00064870
SRO 3.2	• Johnson DJ, Fidock DA, Mungthin M, Lakshmanan V, Sidhu AB, Bray PG, Ward SA. Evidence for a Central Role for PfCRT in Conferring Plasmodium falciparum Resistance to Diverse Antimalarial Agents, Mol Cell 15: 867-77, 2004. • Martin RE, Kirk K. The Malaria Parasite's Chloroquine Resistance Transporter is a Member of the Drug/Metabolite Transporter Superfamily. Mol Biol Evol 21: 1938-49, 2004.
SRO 3.3	Search http://crisp.cit.nih.gov/ for the following grant numbers: • 1U01DE016267-01 • 1U01DE016274-01 • 1U01DE016275-01
SRO 3.4	Source for RV144: http://www2.niaid.nih.gov/Newsroom/Releases/rv144.htm Source for HVTN 040: http://www.hvtn.org/pdf/trials/prot040-QA.pdf Source for other NIH-sponsored HIV vaccine trials: http://Clinicaltrials.gov Source for a NG site: http://www.iavireport.org/trialsdb/ http://www.novavax.com/news.html
SRO 3.2.1	Karin Lohman, NIAID, Office of Policy Analysis, 301-496-6752.
SRO 4.1	Gowan BB et al., Interferon alfacon-1 protects hamsters from lethal Pichinde virus infection. Manuscript in preparation, 2004.

	1 SOURCE VALIDATION 1
	Juvaris BioTherapeutics Announces Evaluation Of Products For Antiviral Application, BioSpace, http://biospace.com/news story.cfm?StoryID=17668920&full=1, 2004. Animal Models of Human Viral Infections for Evaluation of Experimental Therapies, IMEX Buy/Sell Exchange, http://imex.worldbid.com/tradeleads/details.htm?session=&searchwords=&latest=&country=&stars=&all=&bodies=&subcat=29&bidID=507035&type=Buy&m=0, 2004. Jarrett CO et al., Flea-borne transmission model to evaluate vaccine efficacy against naturally acquired bubonic plague. Infect Immun, 72:2052-56, 2004. Day CW et al., Effect of interferon inducers on West Nile virus in cell culture and in mouse and hamster animal models. 17th International Conference of Antiviral Research. May 2-6, 2004. J Antiviral Res, 62: A52, 2004. Money JD et al., Modeling hamsters for evaluating West Nile virus therapies. Antiviral Res, 63:41-50, 2004. Olsen AL, Morey JD. Delivery of antiviral immunoglobulins into the CNS for treatment of encephalitic virus. 17th International Conference of Antiviral Research. J Antiviral Res, 62: A32, 2004.
SRO 4.2	The Annual Report from the grantee verifies the target achievement. A copy of the report may be obtained from the NIEHS, NIH, Office of Policy, Planning and Evaluation, Bldg. 101, Rm. B217, Research Triangle Park, NC 27709, tel 919-541-4258 (contact is Janet Guthrie). Literature references: • Greene et al., Proc Natl Acad Sci 100(7):4078-4083, 2003 • Goldberg et al., J Biol Chem 278(44):43628-43635, 2003 • Chandra et al., Proc Natl Acad Sci 101(41):14966-14971), 2004 • McNaught et al., Ann Neurol 56(1):149-162, 2004
SRO 5.1	CHUNG R, ANDERSEN J, VOLBERDING P, ROBBINS G, TUN LIU T, SHERMAN K, PETERS M, KOZIEL M, BHAN K, ALSTON B, COLQUHOUN D, NEVIN T, HARB G, AND VAN DER HORST C. FOR THE A5071 STUDY TEAM: A RANDOMIZED, CONTROLLED TRIAL OF PEG-INTERFERON ALPHA 2-A PLUS RIBAVIRIN VERSUS INTERFERON ALPHA-2A PLUS RIBAVIRIN FOR CHRONIC HEPATITIS C VIRUS INFECTION IN HIV-CO-INFECTED PERSONS: THE U.S. AIDS CLINICAL TRIALS GROUP A5071 STUDY TEAM. NEW ENGLAND JOURNAL OF MEDICINE (IN PRESS). Larsen R, Bauer M, Thomas A and Graybill J: Amphotericin B and fluconazole, a potent combination therapy for cryptococcal meningitis. Antimicrobial Agents and Chemotherapy 48: 985-991, 2004. NIH FISCAL YEAR 2004 PLAN FOR HIV-RELATED RESEARCH, AVAILABLE ONLINE AT HTTP://WWW.NIH.GOV/OD/OAR/PUBLIC/PUBLIC.HTM, 2004. LETENDRE S, MCCUTCHAN J, CHILDERS, M, WOODS S, LAZZARETTO D, HEATON R, GRANT I, ELLIS R, AND THE HNRC GROUP. ENHANCING ANTIRETROVIRAL THERAPY FOR HUMAN IMMUNODEFICIENCY VIRUS COGNITIVE DISORDERS. ANNALS OF NEUROLOGY 56: 416-423, 2004. Lallemant M, Jourdain G, Le Coeur S, Mary JY, Ngo-Giang-Huong N, Koetsawang S, Kanshana S, McIntosh K, and Thaineua V: Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. New England Journal of Medicine 351: 217-28, 2004. DICENZO R, PETERSON D, CRUTTENDEN K, MORSE G, RIGGS G, GELBARD H AND SCHIFITTO G. EFFECTS OF VALPROIC ACID COADMINISTRATION ON PLASMA EFAVIRENZ AND LOPINAVIR C CONCENTRATIONS IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED ADULTS. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 48: 4328-4331, 2004. Weed M, Hienz R, Brady J, Adams R, Mankowski J, Clements J, Zink M. Central nervous system correlates of behavioral deficits following simian immunodeficiency virus infection. Journal of Neurovirology 9(4):452-64, 2003. Bachis A, Major E, Mocchetti I. Brain-derived neurotrophic factor inhibits human immunodeficiency virus-1/gp120-mediated cerebellar granule cell death by preventing gp120 internalization. Journal of Neuroscience 23(13):5715-22, 2003. King N, Prabu-Jeyabalan M, Nalivaika E, Schiffer C. Combating susceptibility to drug resistance: lessons from

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SRO 5.2	Contract N01AR Annual and monthly progress reports retained by NIAMS, NIH, One Democracy Plaza, 6701 Democracy Boulevard, Room 834, Bethesda, MD 20892, tel 301-594-2543 (contact is Eileen Webster-Cissel). Data and Safety Monitoring Board Minutes (April 2004) are retained by NIAMS, NIH, One Democracy Plaza, 6701 Democracy Boulevard, Room 856, Bethesda, MD 20892, tel 301-451-5888 (contact is Dr. Madeline Turkeltaub).
SRO 5.3	• Information on the Chemical Methodologies and Library Development Centers can be found at http://www.nigms.nih.gov/cmld/. • Press release on online resource developed by Boston University CMLD: http://www.eurekalert.org/pub releases/2004-06/bu-bcd060904.php • Press release on the ICBG program: http://www.nih.gov/news/pr/dec2003/fic-16.htm • Press release on NIH Chemical Genomics Center: http://www.nih.gov/news/pr/iun2004/nhgri-09.htm • Information on the UCSD NMR Resource Center: http://nmrresource.ucsd.edu/ • Wipf, P., Stephenson, C.R.J., and Walczak, M.A.A. Diversity-Oriented Synthesis of Azaspirocycles. Org. Lett. 2004, 6, 3009-3012. • Wipf, P., Janjic, J., Stephenson, C.R.J. Microwave-Assisted Synthesis of Allylic Amines: Considerable Rate Acceleration in the Hydrozirconation-Transmetalation-Aldimine Addition Sequence. Org. Biomol. Chem. 2004, 2 , 443-445. • Brummond, K.M., Mitasev, B. Allenes and Transition Metals: A Diverging Approach to Heterocycles. Org. Lett. 2004, 6, 2245. • Zhu C., Shen X., and Nelson S.G. Cinchona AlkaloidLlewis Acid Catalyst Systems for Enantioselective Ketene-Aldehyde Cycloadditions. J. Am. Chem. Soc. 2004, 126, 5352-5353.

SRO 5.4	Neurodegeneration Drug Screening Consortium: • Rescue of a human mRNA splicing defect by the plant cytokinin kinetin. Slaugenhaupt et al. Hum Mol Ge 13(4):429-436, 2004. • A screen for drugs that protect against the cytotoxicity of polyglutamate-expanded androgen receptor. Picc et al. Hum Mol Genet 13(4):437-446, 2004. • A cell-based screen for drugs to treat Huntington's disease. Aiken et al. Neurobiol Dis 16(3):546-55, 2004 • A novel action of histone deacetylase inhibitors in a protein aggresome disease model. Corcoron et al. Cur Biol 14(6):488-92, 2004. • Clinically approved heterocyclics act on a mitochondrial target and reduce stroke-induced pathology. Stavrovskaya et al. J Exp Med 200(2):211-22, 2004. • Use of ceftriaxone for ALS clinical trial: Search http://crisp.cit.nih.gov/ for the following grant number: 1R01NS049640-01 Anticonvulsant Screening Project: • Press release on ICA-69673 is at http://www.icagen.com/pr2003 12 23.htm Other advances are proprieta the NIH commitment to keep company proprietary data confidential has been essential to the success of th public-private partnership. Alcohol abuse and addiction drug screening project: Search http://crisp.cit.nih.gov/ for the following grant numbers: • R01AA010709 • U01AA013522 • U01AA013520 • U01AA013483
SRO 5.5	**http ://www.nida.nih.gov/CTN/Index.htm** **http ://www.seekingsafety.org/7-15-04%20new%20D2s/articles.htm#The%20Seekins%20Safety%20model%20(descriDtion%20and%20imnlementation)** Santisteban, DA., Coatsworth, J.D., Perez Vidal, A., Kurtines, W.M., Schwartz, SW., Laperriere, A., & Szapocznik, J. (2003). "The efficacy of Brief Strategic Family Therapy in modifying Hispanic adolescent behavior problems and substance use." Journal of Family Psychology, 17(1), 121-1 33. Coatsworth, J.D., Santisteban, D.A., McBride, C.K., Szapocznik, J. (2001) "Brief Strategic Family Therapy versus community control: engagement, retention and an exploration of the moderating role of adolescent symptom severity." Family Process, 40(30), 313-332 Santisteban, D.A., Szapocznik, J., Perez-Vidal, A., Kurtines, W.M., Murray, El & Laperriere, A. 1996). Efficacy of intervention for engaging youth and families into treatment and some variables that may contribute to differential effectiveness. Journal of Family Psychology,10(1), 35-44 Carroll, K.M, Farentinos, C., Ball, S.A., Crits-Christopher, P., Libby, B., Morgenstern, J., Obert, J.L., Polcin, D., Woody, G.E. (2002) "MET meets the real world: design issues and clinical strategies in the Clinical Trials Network." Journal of Substance Abuse Treatment, 23, 73-80 Hien, D.A., Cohen, L.R., Miele, G.M., Litt, L.C., Capstick, C. (2004) "Promising Treatments for Women with Comorbid OTSD and Substance Use Disorders." American Journal of Psychiatry 161:8, 14226-1432 Najavits LM (2002). Seeking Safety: A new psychotherapy for posttraumatic stress disorder and substance use disorder. In: Trauma and Substance Abuse: Causes, Consequences, and Treatment of Comorbid Disorders (P. Ouimette & P. Brown, Eds.), pages 147-170. Washington, DC: American Psychological Association Press. Najavits LM. Seeking Safety therapy for trauma and substance abuse. Corrections Today, 2002; 64: 136-140. Godley, M.D., Godley, S.H., Dennis, M.L., Funk, R., Passetti, L.L. (2002) "Preliminary outcomes from the assertive continuing care experiment for adolescents discharged from residential treatment." Journal of Substance Abuse Treatment, 23(1), 21-32

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	Polcin, D.L. (2001) "Sober living houses: potential roles in substance abuse services and suggestions for research." Substance Use & Misuse, 36(3), 301-311 Stout, R.L., Rubin, A., Zwick, W., Zywiak, W., Bellino, L. (1999) "Optimizing the cost-effectiveness of alcohol treatment: a rationale for extended case monitoring." Addictive Behaviors, 24(1), 17-35 Majer, J.M., Jason, L.A., Ferrari, J.R., Venable, L.B., Olson, B.D. (2002) "Social support and self-efficacy for abstinence: is peer identification an issue?" Journal of Substance Abuse Treatment, 23(3), 209-215 McGillicuddy, N.B., Rychtarik, Duquette, J.A., Morsheimer, E.T. (2001) "Development of a skill training program for parents of substance-abusing adolescents." Journal of Substance Abuse Treatment, 20(1), 59-68 McGillicuddy, N.B., Rychtarik, R.G., Morsheimer, E.T. (2004) "Psychometric evaluation of the parent situation inventory: a role-play measure of coping in parents of substance-using adolescents." Phychological Assessment, 16(4), 386-389 Brochures: "Clinical Trials Network: Women's Treatment for Trauma and Substance Use Disorders: A research study for women dealing with trauma and substance abuse. For Clinicians" NIDA 2004 "Clinical Trials Network: Women's Treatment for Trauma and Substance Use Disorders: A research study for women dealing with trauma and substance abuse. Should I sign up?" NIDA 2004 "Clinical Trials Network: Motivational Enhancement Therapy: A research study on preparing people for change: Should I join the Motivational Enhancement Therapy?" NIDA 2004 "Clinical Trials Network: Motivational Enhancement Therapy: A research study on preparing people for change. For Clinicians." NIDA 2004 "Clinical Trials Network: Brief Strategic Family Therapy for Adolescent Drug Abusers: A research study involving the family. For Clinicians" NIDA 2004 "Clinical Trials Network: Brief Strategic Family Therapy for Adolescent Drug Abusers: A research study involving the family. Should I sign up?" NIDA 2004 "Clinical Trials Network: Brief Strategic Family Therapy for Adolescent Drug Abusers: A research study involving the family. Sholuld we sign up? Information for Parents" NIDA 2004
SRO 6.1	A meeting summary can be found at http://www.nei.nih.gov/strategicplanning/amd meeting.asp
SRO 6.2	NIH has a letter from the lead investigator for the Look AHEAD coordinating center stating that the trial completed recruitment on April 30, 2004; it may be obtained by calling the Office of Science Program and Policy Analysis at 301-496-6623 (contact is Dr. Patrick Donohue). URLs for the clinical trials: • Look AHEAD: http://www.clinicaltrials.gov/ct/show/NCT00017953 • ACCORD: http://www.clinicaltrials.gov/ct/show/NCT00000620 • BARI 2D: http://www.clinicaltrials.gov/ct/show/NCT00006305 • FAVORIT: http://www.clinicaltrials.gov/ct/show/NCT00064753 • FREEDOM: http://www.clinicaltrials.gov/ct/show/NCT00086450
SRO 6.3	The CEBS website http://cebs.niehs.nih.gov/ confirms the functionality of CEBS. Publication in support of CEBS SysBio-OM: Xirasagar S, Gustafson S, Merrick BA, Tomer KB, Stasiewics S, Chan DD, Yost KJ, Yates JR, Sumner S, Xiao N, and Waters MD. CEBS object model for system biology data, SysBio-OM. Bioinformatics 20(13):2004-15, 2004
SRO 7.1	The results of all studies cited here have been published in peer reviewed scientific journals: • Donovan JL, et al. Green tea (Camellia sinensis) extract does not alter cytochrome P-450 3A4 or 2D6 activity in healthy volunteers. Drug Metab Dispos. 2004 Jun 9 [Epub ahead of print] • Gorski JC, et al. The effect of echinacea (Echinacea purpurea root) on cytochrome P450 activity in vivo. Clin Pharmacol Ther. 2004 Jan;75(1):89-100. • Ma Y, et al. Desmethoxyyangonin and dihydromethysticin are two major pharmacological kavalactones with marked activity on the induction of cytochrome P4503A23. Drug Metab Dispos. 2004 Jul 28 [Epub ahead of

GOAL 1	SOURCE VALIDATION		
	print].		
SRO 7.2	National Characterization Laboratory Business Plan. Please contact Dr. Gregory Downing, Director, Office of Technology and Industrial Relations, NCI, 31/10A52, phone: 301-402-5079, fax: 301-496-7807, downing@mail.nih.gov, for a copy of the plan.		
SRO 7.3	The SNP Database can be found at http://www.ncbi.nlm.nih.gov/SNP/ The contact for the SNP database is: Stephen Sherry, PhD National Center for Biotechnology Information National Library of Medicine 45 Center Drive, MSC 6510, Bethesda, MD 20892-6510 phone: (301) 435-7799 sherry@ncbi.nlm.nih.gov fax: (301) 480-2484		
SRO 8.1	Organism	Reference	URL for Sequence Data
	Aspergillus fumigatus		http://www.tigr.org/tdb/e2k1/afu1/
	Bacillus anthracis-4 strains	Pearson T, Busch JD, Ravel J, Read TD, Rhoton SD, U'Ren JM, Simonson TS, Kachur SM, Leadem RR, Cardon ML, Van Ert MN, Huynh LY, Fraser CM and Keim P: Phylogenetic discovery bias in Bacillus anthracis using single nucleotide polymorphisms from whole genome sequencing. PNAS 101: 13536-13541, 2004.	
	Bacillus cereus-1 strain CDC G9241	Hoffmaster AR, Ravel J, Rasko DA, Chapman GD, Chute MD, Marston CK, De BK, Sacchi CT, Fitzgerald C, Mayer LW, Maiden MC, Priest FG, Barker M, Jiang L, Cer RZ, Rilstone J, Peterson SN, Weyant RS, Galloway DR, Read TD, Popovic T, and Fraser CM: Identification of anthrax toxin genes in a Bacillus cereus associated with an illness resembling inhalation anthrax. PNAS 101:8449-8454, 2004.	
	Candida albicans	Genbank accession # NC_002653	http://www-sequence.stanford.edu/group/candida/
	Clostridium perfringens SM101	Genbank accession # NC_003913	
	Cryptococcus neoformans (B3501)	Genbank accession # AAEY00000000	
	Cryptococcus neoformans (JEC21)		http://www.tigr.org/tdb/e2k1/cna1/

	Cryptosporidium hominis	Xu P, et al: The genome of Cryptosporidium hominis. Nature 431:1107-1112, 2004. Corrigendum: The genome of Cryptosporidium hominis. Nature 432:415, 2004. Genbank accession # AAEL00000000	
	Entamoeba histolytica		http://www.tigr.org/tdb/e2k1/eha1/
	Legionella pneumophila	Chien et al: The Genomic Sequence of the Accidental Pathogen Legionella pneumophila. Science 305: 1966-1968, 2004.	
	Mycobacteria smegmatis	Genbank accession # NC_002974	
	Toxoplasma gondii		http://www.tigr.org/tdb/e2k1/tga1/
	Treponema denticola	Genbank accession # NC_002967	http://www.nidcr.nih. gov/NewsAndReports/NewsReleasesZNewsRelease03292004.htm
	Trypanosoma brucei	Genbank accession # NC_005063	
	Prevotella intermedia	Genbank accession #NC 003441	
	Fusobacterium nucleatum	Genbank accession # AE009951	http://www.hgsc.bcm.tmc.edu/proiects/microbial/Fnucleatum/ http://www.ncbi.nlm.nm.gov/genomes/chromxgi?db=G&gi=233
	Actinomycetes naeslundii		http://tigrblast.tigr.org/ufmg/index.cgi7database=a naeslundii|seq
	Bacteroides forsythus		http://tigrblast.tigr.org/ufmg/index.cgi7database=b forsythus|seq
	Streptococcus gordonii		http://tigrblast.tigr.org/ufmg/index.cgi7database=s gordonii|seq
	Streptococcus mitis		http://tigrblast.tigr.org/ufmg/index.cgi7database=s mitislseq
	Streptococcus sanguis		http://www.sanguis.mic.vcu.edu/sequence data. htm

	Streptococcus sobrinus		http://tigrblast.tigr.org/ufmg/index.cgi?database=s sobrinusjseq
SRO 8.2	The work on osteonectin-cell interactions is described in the Grant Progress Report submitted by the University of Connecticut Health Center as part of the application for continued funding of this project. The Grant Progress Report is part of the official file on grant number 7R01AR044877-07 (find abstract for grant number 7R01AR044877-07 in http://crisp.cit.nih.gov/), which is maintained by NIAMS, NIH, One Democracy Plaza, 6701 Democracy Boulevard, Room 834, Bethesda, MD 20892, tel 301-594-2543 (contact is Eileen Webster-Cissel). Biglycan work: Chen et al. FASEB Journal (Vol. 18, pp. 948-958, 2004)		
SRO 8.3	Inclusion of the RefSeq collection in the Entrez Gene database serves to verify that the FY2004 performance target was met. The inclusion of RefSeq records in Entrez Gene is indicated in a FTP report: ftp://ftp.ncbi.nih.gov/gene/DATA/gene2refseq.gz The Entrez Gene resource was announced in the NCBI newsletter, on NCBI web pages, and by email to a subscribed user-group. The resource is available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene see www.ncbi.nlm.nih.gov/RefSeq/collaborators.html for list of over 20 collaborations The Entrez Gene resource and RefSeq collection are also described in the following publications: Pruitt, K., Tatusova, T., Maglott, D. NCBI Reference Sequence (RefSeq): a curated non-redundant sequence database of genomes, transcripts, and proteins. Nucleic Acids Research, in press Maglott, D., Ostell, J., Pruitt, K., Tatusova, T. Entrez Gene: Gene-centered information at NCBI Nucleic Acids Research, in press		
SRO 8.4	A copy of the final report titled "Feasibility Study for the COBRE Program Evaluation, Final Report" can be obtaine from the Office of Science Policy and Public Liaison, NCRR, One Democracy Plaza, 6701 Democracy Boulevard, Room 985, Bethesda, Maryland 20892-4874, tel 301-435-0866 (contact is Patricia Newman). All of the informational received through the data collection and management system can be found in the Annual Progress Reports (APR) received from each BRIN grantee. The Annual Progress Reports are filed in the Office of Grants Management, NCRR, One Democracy Plaza, 6701 Democracy Boulevard, Room 1061, Bethesda, Maryland 20892-4874, tel 301-435-0844 (contact is Irene Grissom).		

GOAL II	SOURCE VALIDATION
SRO 9.1	• http://dukemednews.org/news/article.php?id=626 • Taylor WD, MacFall JR, Payne ME, McQuoid DR, Provenzale JM, Steffens DC, Krishnan KR. Late-life depression and microstructural abnormalities in dorsolateral prefrontal cortex white matter. Am J Psychiatry. 2004 Jul;161(7):1293-6. • Si X, Miguel-Hidalgo JJ, O'Dwyer G, Stockmeier CA, Rajkowska GAge-Dependent Reductions in the Level of Glial Fibrillary Acidic Protein in the Prefrontal Cortex in Major Depression. Neuropsychopharmacology. 2004 Jul 7 • Krishnan KR, Taylor WD, McQuoid DR, MacFall JR, Payne ME, Provenzale JM, Steffens DC. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. Biol Psychiatry. 2004 Feb 15;55(4):390-7. • Taylor WD, Steffens DC, MacFall JR, McQuoid DR, Payne ME, Provenzale JM, Krishnan KR.White matter hyperintensity progression and late-life depression outcomes.Arch Gen Psychiatry. 2003 Nov;60(11):1090-6. • Levy RM, Steffens DC, McQuoid DR, Provenzale JM, MacFall JR, Krishnan KR.MRI lesion severity and mortality in geriatric depression.Am J Geriatr Psychiatry. 2003 Nov-Dec;11(6):678-82. • Steffens DC, Taylor WD, Krishnan KR.Progression of subcortical ischemic disease from vascular depression to vascular dementia.Am J Psychiatry. 2003 Oct;160(10):1751-6. • Vythilingam M, Charles HC, Tupler LA, Blitchington T, Kelly L, Krishnan KR.Focal and lateralized subcortical abnormalities in unipolar major depressive disorder: an automated multivoxel proton magnetic resonance spectroscopy study.Biol Psychiatry. 2003 Oct 1;54(7):744-50. • Lee SH, Payne ME, Steffens DC, McQuoid DR, Lai TJ, Provenzale JM, Krishnan KR.Subcortical lesion severity and orbitofrontal cortex volume in geriatric depression.Biol Psychiatry. 2003 Sep 1;54(5):529-33. • Rajkowska G.Depression: what we can learn from postmortem studies.Neuroscientist. 2003 Aug;9(4):273-84. • Taylor WD, MacFall JR, Steffens DC, Payne ME, Provenzale JM, Krishnan KR.Localization of age-associated white matter hyperintensities in late-life depression.Prog Neuropsychopharmacol Biol Psychiatry. 2003 May;27(3):539-44. • Taylor WD, McQuoid DR, Krishnan KR. Medical comorbidity in late-life depression.Int J Geriatr Psychiatry. 2004 Oct;19(10):935-43. • Si X, Miguel-Hidalgo JJ, O'Dwyer G, Stockmeier CA, Rajkowska G. Age-dependent reductions in the level of glial fibrillary acidic protein in the prefrontal cortex in major depression. Neuropsychopharmacology. 2004 Nov;29(11):2088-96.
SRO 9.2	"NIH, Washington Hospital Center Acute Stroke Research Program Moving Forward" Washington Hospital Center Neuroscience Institute Clinical Update, Vol. 2, No. 2 - Spring 2004, pp. 6-7. See: http://www.whcenter.org/centersframe.cfm?id=1445 "Washington Hospital Center, National Institutes of Health Collaborate on Acute Stroke Research Project" Press Release, January 5, 2004. See:http://www.whcenter.org/body.cfm?xxx=0&id=337&action=detail&ref=122

COMMUNICATION AND TRANSFER OF RESULTS

GOAL II	SOURCE VALIDATION
CTR-1	SIDS Summits Cross-Site Evaluation Report, Draft 3, 09/29/04, Contact Andrea, Furia. Back to Sleep Campaign National Institute of Child Health and Human Development (301)-435-3459
CTR-2	NINDS Warehouse Inventory -Quarterly Cost Recovery Report NINDS Warehouse Inventory -Quarterly Know Stroke Materials Report Contact

	Marian Emr, Director, Office of Communication and Public Liaison. National Institute of Neurological Disorders and Stroke (301)-496-5924
CTR-3	Project documentation, journal links to "Partnership in technology transfer—an innovative program to enhance biomedical research and global health" (Jan 05) , internal and external communications can, where approved, be obtained by contacting: Contact : Ansalan E. Stewart, Ph.D., Technology Transfer Policy Specialist Office of Technology Transfer, (301)-435-5146
CTR-4	CAP: RFQ No. NLM 04-103 and Contract Number N01-LM-4-5509 Niche Assessment Program: Purchase Order N01-LM-4-5510 (pilot program) Contact: Kay Etzler, SBIR/STTR Program Office of Extramural Programs (301)-435-2713

CAPACITY BUILDING AND RESEARCH RESOURCES

GOAL 1	SOURCEVALIDATION
CBRR-1	"Outcome Evaluation of the NIH National Research Service Award (NRSA) Postdoctoral Training Program." PO #: 467-FZ-402097 Contact Bill McGarvey, Ph.D., Scientific Program Evaluation Specialist Office of Extramural Programs (301)-435-2691
CBRR-2	All project performance metrics and associated communications are stored in the NBS project database. Contact Nancy Parfitt-Hondros NBS Project Management Office Office of Extramural Programs (301)-451-0005
CBRR-3	OMB 300 filings, CRIS Steering Committee minutes. Medical Executive Committee minutes. ID: 000-25-01-06-01¬ 3006-00-110-219. Contact Elaine Ayres Center for Information Technology (301)-5940-3019
CBRR-4	All project performance metrics and associated communications are stored in the eRA project database. Contact Donna J. Frahm, PMP Chief, Project Management Office Extramural Research Administration (301)-594-9747

STRATEGIC MANAGEMENT OF HUMAN CAPITAL

IGOAL II	SOURCEVALIDATION I
SMHC-3	Report, NIH Office of Intramural Research Study of Recruitment, Development and Succession Planning Practices, July 2004 Contact person Dan Dupuis, Senior Strategic Management Planner Office of Strategic Management Planning (301)-402-0622
SMHC-4	Transition services: OSMP website at http://osmp.od.nih.gov/NIHTransitionCenter.asp Competitive studies: OMB Report to Congress on FY 2004 Competitive Sourcing Efforts and HHS Quarterly Report submissions.

	PMA Green status: http://www.whitehouse.gov/results/agenda/scorecard.html
SMHC-5	No activities (planned or initiated) in FY2004 to report

PROGRAM OVERSIGHT AND IMPROVEMENT

GOAL 1	SOURCE VALIDATION
POI-1	Humphreys & Associates, Inc. Preliminary Report. Contact: Clarence Dukes Program Manager, Federal Programs Office of Research Facilities, Division of Policy & Program Assessment (301)-496-5078
POI-2	PBC activity is validated through reports of PBC funding activity entered by Contracting Offices into an NIH proprietary system. Contact: Shirley Mizzell Acting Director, Division of Acquisition Policy and Evaluation Office of Acquisition Management and Policy Phone (301)496-6014
POI-4	Contact: Susan Kauble Asst Grant Compliance Officer Office of Policy for Extramural Research Administration Phone (301) 451-4351

PERFORMANCE MEASUREMENT LINKAGES

(WITH COST ACCOUNTING, INFORMATION TECHNOLOGY PLANNING, CAPITAL PLANNING, AND PROGRAM EVALUATION)

Cost Accounting

NIH develops and reports the cost of its program on its audited Statement of Net Costs, as required by the CFO Act, the GMRA, and the Office of Management and Budget. These reported costs are derived using an accrual basis of accounting as required by federal accounting standards and the Federal Financial Management Improvement Act. These amounts differ from the reported obligations or budgetary resources included in budget documents that use an obligation basis of accounting.

NIH includes cost measures for performance goals, as appropriate, in its service and supply fund activities. NIH finances these activities using a fee for service cost recovery method. NIH develops cost per unit of goods or services and benchmarks these unit costs with other providers of similar or complementary goods and services. Also, NIH strives to increase stakeholder value by reducing the cost per unit of goods or services wherever possible.

Information Technology Planning

Information Technology (IT) plays an important role in contributing to the success of the NIH mission to uncover new knowledge about the prevention, detection, diagnosis, and treatment of disease and disability. IT supports the research done in NIH laboratories and grantee institutions as well as supports the training of research investigators, the communication of medical information, and the management of research and administrative activities. The responsibility for the enterprise systems involves a partnership between the functional area manager/program official, who serves as the business owner, and the Chief Information Officer (CIO). The enterprise systems dovetail with the DHHS Enterprise Information Technology Strategic Plan. NIH manages its IT activities in accordance with the Secretary's vision of managing DHHS IT on an enterprise basis.

In recent years NIH has established and strengthened a governance structure that focuses the IT activities of the agency on the NIH mission and institutionalizes a corporate-wide perspective in the management of the IT function. The accomplishment of the IT-specific goals began in 1996, when the NIH Director began activities for managing selected elements of IT from a corporate-wide perspective. His first step addressed the organizational structure by hiring a CIO and the second established the Center for Information Technology (CIT). In addition, two advisory groups were established: the NIH Director formed NIH's IT Board of Governors (BOG), composed of selected senior management from across NIH, and the NIH Director established the NIH IT Working Group (ITWG), composed of senior Institute and Center (IC) representatives, as well as the CIO.

The ITWG's purpose is to (1) review and make recommendations on the IT activities and priorities of the NIH and (2) assess and advocate resources to implement those priorities. These recommendations are forwarded to NIH's Steering Committee for final decision-making. Since then, the CIO and the CIT advisory groups have developed a process for managing IT from a corporate-wide perspective to make it more effective in supporting the mission of NIH and in providing integrated systems that support the variety of NIH business processes. They accomplished the following:

- Strengthened the investment review process and associate training.
- Established a formal project management structure for enterprise IT (Phase I complete)
- Refined and implemented the strategic, corporate "IT vision" for NIH
- Developed an NIH-wide information security program, directed by the IT Management Committee (ITMC)
- Developed interoperability standards (through the Architecture Management Group (AMG) to support wireless networking)

In addition, guidance was developed to assist the ICs in establishing performance measures and evaluating IT programs based on performance measures, (which can be found at http://www.cit.nih.gov/mgmt-pol.asp Discussions of performance measures were woven throughout the Investment Review process described at http://irm.cit.nih.gov/itmra/invreview.html and were also incorporated in the IT Management Guide, http://irm.cit.nih.gov/itmra/mgtprocess.html. Now, when IC program managers conduct a business case analysis, they are advised to address IT performance measures among others. Resources and tools were made available to facilitate this process and can be found at http ://irm.cit.nih.gov/itmra/perfmeasure.html. In addition, the Office of the CIO initiated a recurring class in performance measures, to increase the number of IT and program managers familiar with the creation and use of performance measures.

Having set these organizations, processes, guidelines and tools in place, NIH has focused its Information Technology planning on pursuing the mission of the NIH as described in this Plan/Report. This accomplishment has also enhanced our ability to accomplish the IT-related goals within our core programs in conformance with the performance measurement principles of GPRA.

Capital Planning
In accordance with OMB Circular A-11, Part 6, for FY 2004 and beyond, the NIH Capital Asset Plan (required under Part 7 of OMB Circular A-11) is hereby incorporated in the GPRA Plan/Report (Appendix under Tab 10; see also separate Buildings and Space Plan).

Evaluation
Evaluation is the foundation of managing for results. Inevitably, program managers and other decision-makers gather information about a program and make judgments about its worth or value. The quality of those judgments depends on the quality of the information upon which they are based. For that reason, NIH program managers depend on two complementary evaluation activities, *performance measurement* and *program evaluation,* to establish reasonable performance goals and to accurately assess progress toward those goals.

Performance measurement refers to regular monitoring of program accomplishments. Program accomplishments include the activities conducted (process), products produced or services delivered (outputs), and the results of those products and services (outcomes). Performance measurement is conducted by program managers to gauge how well the program is progressing toward its intended goals. The information gained from such on-going tracking systems may alert program managers to emerging problems and may spur a program evaluation to provide more information on why the program is not achieving anticipated results.

Program evaluation refers to systematic investigations or studies that involve assessing the worth and/or performance of particular programs. In most cases, the underlying purpose of a program evaluation is to help program managers answer specific questions about a program, such as whether it is being implemented as planned or is achieving its intended purpose. Managers typically use the information obtained from program evaluations to understand why certain results are or are not being achieved and to make adjustments in program strategies or activities. The four types of program evaluations conducted by NIH are needs assessments, feasibility studies, process evaluations, and outcome evaluations. Needs assessments and feasibility studies are usually conducted as preliminary studies (e.g., to improve the design of a more complex process or outcome evaluation). Experts external to the program often conduct program evaluations, but program managers may also conduct them.

Purposes of Program Evaluation under GPRA
At NIH, program evaluation serves two important purposes under GPRA: to support program planning and to support program performance assessment.

Support Program Planning. Program evaluations provide useful information to NIH's program managers regarding the appropriateness of established performance goals, annual targets, and implementation strategies. For example, needs assessments are typically conducted to identify systematically whom a program is serving and the extent to which their needs are being addressed. Needs assessments also may explain why certain needs are not being met and how the program could be revised to address the unmet needs. Using the information gained from such evaluations as a foundation for program planning, NIH program managers develop and modify performance goals and targets to more effectively direct their programs toward the desired outcomes. In addition, the strategies used to implement NIH programs are often adjusted based on evaluation findings.

Support Program Performance Assessment. Program evaluations support program performance assessment activities at NIH primarily by providing insight regarding the relationship between NIH activities and the results NIH seeks to achieve. Outcome evaluations are often conducted to obtain methodologically sound information about the effectiveness of a program and to measure the program's progress towards goal achievement. In addition, this information is critical to determining the extent to which a program's activities contributed to any measured progress toward the desired end result or outcome.

NIH managers also use process evaluations to examine program progress (as evidenced primarily by program outputs) and to determine whether programs are being implemented as planned. The information gleaned from these evaluations allows managers to make midcourse corrections and improve program administration. Finally, feasibility studies are used to develop better ways to measure program performance. Examples include developing databases to track information over time, identifying ways to more effectively access existing data sources, developing new data collection instruments, and validating/verifying data sources.

Program: *HIV/AIDS Research*

Rating: *Moderately Effective*

Agency: Department of Health and Human Services
Bureau: National Institutes of Health

Program Type: Research and Development

Last Assessed: 1 year ago

Key Performance Measures from Latest PART	*Year*	*Target*	*Actual*
Long-term Measure: By 2010 develop an HIV/AIDS vaccine. 2005 Target: Expai breeding of non-human primates at 3 Centers. 2006 Target: Initiate 1 new Phase lib trial to determine if a third generation vaccine candidate has efficacy. 2007 Target: Continue development and evaluation of candidate vaccines.	2005	3 Primate Centers	
	2006	1 Phase lib Trial	
	2007	Dvlp/Eval Candidate	
	2010	1 Vaccine	
Long-term Measure: By 2007 evaluate the efficacy of 3 new treatments. 2005 Target: Develop 3 anti-HIV compounds. 2006 Target: Evaluate interventions to reduce mother-to-child transmissioi (MTCT) of HIV and assess the impact of these interventions on future treatment options for women and children.	2005	3 Compoun	
	2006	Eval MTCT	
	2007	3 new treatment	

Recommended Follow-up Actions from Latest PART	*Status*
Adopt the revised goal of extending the timeline for developing an AIDS vaccine from 2007 to 2010, to more realistically reflect the state of the science.	**Completed**
Develop targets for the revised goal.	**Completed**

Update on Follow-up Actions:

Program Funding Level (in millions of dollars)

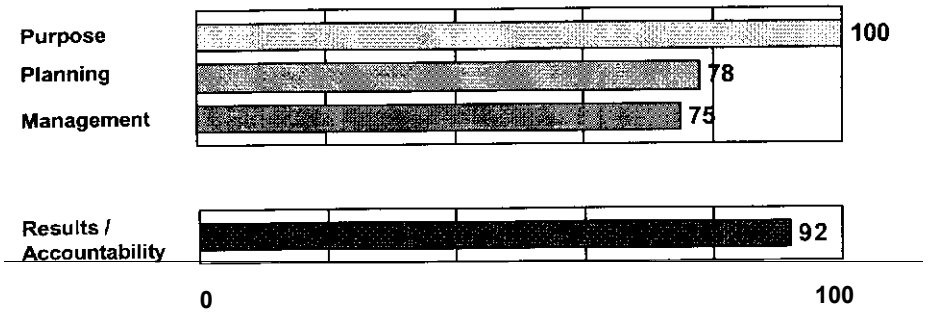
2004 Actual	2005 Estimate	2006 Estimate
2,850	2,920	2,933

Program: *NIH Extramural Research Programs*

Rating: *Effective*

Agency: Department of Health and Human Services
Bureau: National Institutes of Health

Program Type: Research and Development



Program Summary:

To encourage and support research activities related to detection, diagnosis, treatment, rehabilitation, and prevention of disease and disorders, the National Institutes of Health (NIH) is authorized to make grants and enter into contracts and cooperative agreements. NIH's Extramural Research program touches on 238 disease areas, emerging public health threats, new technologies, and novel approaches, and is designed to use merit-based peer review to support grant funding decisions. The program funds a wide spectrum of activities such as basic research, research instruments and equipment, publicly accessible databases, specimen and tissue repositories, animal resources, early stage clinical trials, and development of treatment guidelines. Typically the program's research areas are not conducted by the private sector.

The assessment found that the program is working well overall, but there are areas for improvement. Additional findings include:

- **NIH is unique in that it is the only agency, governmental or private, that has a broad mission of improving the Nation's health through funding biomedical and behavioral research.**
- **The Extramural Research program has as its core the merit-based peer review process, followed by oversight by Institute and Center advisory councils, which allow NIH to fund meritorious grants with the potential for discovery.**
- **Priorities are developed during NIH's annual budget formulation process, which can include annual strategic planning sessions. These priorities are based on scientific importance/relevance, emerging public health threats, and potential public health benefits.**
- **The program has a limited number of specific long-term performance goals and annual targets that focus on outcomes.**
- **Until NIH's New Business System and the HHS-wide system are fully deployed, the preparation of financial statements will continue to be manually intensive and time consuming.**

In response to these findings, the Administration will:

1. **Continue to monitor efforts to implement new financial management practices and systems.**
2. **Work to improve its monitoring of grants to ensure awardees are achieving stated goals and able to display results.**

Key Performance Measures from Latest PART	*Year*	*Target*	*Actual*
Long-term Measure: By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point of new drugs.	2006	SMR	
	2007	Models	
	2008	ID 4	
	2009	ID 10	
Long-term Measure: 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.	2006	Rpt Trial	
	2007	Recru. 4K	
	2008	Phase 2	
	2011	Rpt Trial	
Long-term Measure: By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease.	2006	Recuit 1K	
	2007	ID AD Sx	
	2008	ID lead	
	2012¬ 2013	Interven.	

Program Funding Level (in millions of dollars)

2004 Actual	2005 Estimate	2006 Estimate
20,880	21,146	21,385

PART RECOMMENDATIONS FY 2004-2006

FY 2005 - HIV/AIDS Research

NIH			
Recommendation 1	**Completion Date**	**On Track? (Y/N)**	**Comments on Status**
BY 2010, DEVELOP AN HIV/AIDS VACCINE.	FY 2010	Yes	Annual Target Met
Next Milestone	**Next Milestone Date**	**Lead Organization**	**Lead Official**
Initiate one to two multinational trials in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.	Completed FY 2004	NIH	Wendy Wertheimer/ Deborah Duran
1) Expand breeding of non-human primates: 3 centers; 2) Test 1 new virus stock; 3) Test 2 vaccine candidates in animals; 4) Phase I human trials: 1 vaccine candidate; 5) Seroincidence data: 3 sites; 6) Evaluate vaccine safety: 2labs; 7) Initiate 4 phases 1 and II vaccine trials; 8) Produce candidate vaccine for phase III trials.	FY 2005	NIH	Wendy Wertheimer/ Deborah Duran
Initiate 1 new Phase IIb trial to determine if a third generation vaccine candidate has efficacy.	FY 2006	NIH	Wendy Wertheimer/ Deborah Duran
Continue development and evaluation of candidate vaccines.	FY 2007	NIH	Wendy Wertheimer/ Deborah Duran

Recommendation 2	**Completion Date**	**On Track? (Y/N)**	**Comments on Status**
BY 2007, EVALUATE THE EFFICACY OF THREE NEW TREATMENT STRATEGIES FOR HIV INFECTION IN CLINICAL TRIALS IN AN EFFORT TO IDENTIFY AGENTS OR COMBINATIONS OF AGENTS THAT ARE MORE EFFECTIVE, LESS TOXIC, AND/OR SIMPLER TO USE THAN THE CURRENT RECOMMENDED HIV TREATMENT REGIMENS.	FY 2007	Yes	Annual Target Met
Next Milestone	**Next Milestone Date**	**Lead Organization**	**Lead Official**
Participate in the development of two agents for the prevention or treatment of HIV-associated manifestations, such as co-infections, opportunistic infections, cancers, neurological disorders, or organ-specific complications.	Completed FY 2004	NIH	Wendy Wertheimer/ Deborah Duran
1) Develop 3 anti-HIV compounds; 2) Initiate 4 drug clinical trials; 3) Develop/test 2 agents to prevent/treat drug complications; and 4) Develop/test 1 new approach to inhibit mother-to-child transmission.	FY 2005	NIH	Wendy Wertheimer/ Deborah Duran
Evaluate interventions to reduce mother to child transmission (MTCT) of HIV and assess the impact of these interventions on future treatment options for women and children.	FY 2006	NIH	Wendy Wertheimer/ Deborah Duran

FY 2006 Extramural Research

Recommendation 1	Completion Date	On Track? (Y/N)	Comments on Status
BY 2009, EXPAND THE RANGE OF AVAILABLE METHODS USED TO CREATE, ANALYZE AND UTILIZE CHEMICAL LIBRARIES, WHICH CAN BE USED TO DISCOVER NEW MEDICATIONS. SPECIFICALLY, USE THESE CHEMICAL LIBRARIES TO DISCOVER 10 NEW AND UNIQUE CHEMICAL STRUCTURES THAT COULD SERVE AS THE STARTING POINT OF NEW DRUGS.	FY 2009	Yes	Annual Target Met
Next Milestone	**Next Milestone Date**	**Lead Organization**	**Lead Official**
Participate in the development of two agents for the prevention or treatment of HIV-associated manifestations, such as co-infections, opportunistic infections, cancers, neurological disorders, or organ-specific complications.	Completed FY 2004	NIH	Jim Onken/ Deborah Duran
Initiate clinical trials of new anti-HIV drugs and/or anti-HIV multi-drug regimens in U.S. and international clinical trial sites.	FY 2005	NIH	Jim Onken/ Deborah Duran
Evaluate interventions to reduce mother to child transmission (MTCT) of HIV and assess the impact of these interventions on future treatment options for women and children.	FY 2006	NIH	Jim Onken/ Deborah Duran

Recommendation 2	Completion Date	On Track? (Y/N)	Comments on Status
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.	FY 2011	Yes	Annual Target Met
Next Milestone	**Next Milestone Date**	**Lead Organization**	**Lead Official**
Complete recruitment for the Action for Health in Diabetes (Look AHEAD) study (5,000 patients), in order to compare the effects on cardiovascular events of an intensive lifestyle intervention designed to achieve and sustain weight loss versus support and education in obese individuals with type 2 diabetes.	Completed FY 2004	NIH	Carol Feld/ Deborah Duran
Complete recruitment for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (10,000 patients), which is comparing effects on CVD of intensive versus conventional interventions of lowering blood glucose, blood pressure; and treating blood lipids in diabetic patients at high risk for CVD.	FY 2005	NIH	Carol Feld/ Deborah Duran
Look AHEAD aims to report outcome data on the success of the one-year intensive weight loss intervention and its impact on CVD risk factors such as diabetes control, lipids, blood pressure, and fitness.	FY 2006	NIH	Carol Feld/ Deborah Duran

Recommendation 3	Completion Date	On Track? (Y/N)	Comments on Status
BY 2013, IDENTIFY AT LEAST ONE CLINICAL INTERVENTION THAT WILL DELAY THE PROGRESSION, DELAY THE ONSET, OR PREVENT ALZHEIMER'S DISEASE (AD).	FY 2013	Yes	Annual Target Met
Next Milestone	**Next Milestone Date**	**Lead Organization**	**Lead Official**
Identify and implement effective strategies to facilitate drug discovery and development for AD treatment and prevention in collaboration with relevant organizations, as well as through stimulation of relevant research through Program Announcements and/or other mechanisms.	Completed FY 2004	NIH	Lorraine Fitzsimmons/ Deborah Duran
Launch the Alzheimer's Disease Neuroimaging Initiative to evaluate neuroimaging modalities and techniques and other biomarkers to be used in early diagnosis, follow the progression of mild cognitive impairment (MCI) and AD, and use as potential surrogate markers for drug development and clinical trials.	FY 2005	NIH	Lorraine Fitzsimmons/ Deborah Duran
Identify around 1,000 new late onset AD families to allow geneticists to locate additional late onset risk factor genes for AD that may lead to new targets for drug treatment, and provide a well-characterized population for more efficient clinical trials.	FY 2006	NIH	Lorraine Fitzsimmons/ Deborah Duran

SUMMARY OF MEASURES

MEASURES AND RESULTS SUMMARY TABLE									
Fiscal Year	**Goals** (long-term measures)				**Targets** (annual measures)				
	Total	**Outcome**	**Output**	**Efficiency**	**Total**	**Reported**	**Met**	**Not Met**	**Extended**
2002	40	NA	NA	NA	79	79	66	2	11
2003	36	28	8	12	47	47	39	0	8
2004	41	30	11	11	54	56	52	1	3
2005	49	37	12	10	57	Performance will be reported in February 2006.			
2006	39	26	13	8	50	Performance will be reported in February 2007.			

NA = Not applicable
Extended targets may increase the reported column in relation to the total targets for the given year.