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SUMMARY OF RESEARCH ACTIVITIES BY KEY APPROACH AND RESOURCE

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Volume III Contents

Chapter 3: Summary of Research Activities by Key Approach and Resource

Fields and Approaches

Epidemiological and Longitudinal Studies	3-1
Genomics.....	3-27
Molecular Biology and Basic Sciences	3-55
Clinical and Translational Research.....	3-103

Tools and Training

Disease Registries, Databases, and Biomedical Information Systems	3-185
Technology Development.....	3-211
Research Training and Career Development.....	3-247

Health Information and Communication

Health Communication and Information Campaigns and Clearinghouses.....	3-271
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Contents of Other Volumes

Volume I

Preface
Chapter 1: About NIH

Volume II

Chapter 2: Summary of Research Activities by Disease Category

Volume IV

Chapter 4: NIH Centers of Excellence

Volume V

Chapter 5: Appendices
Index

Epidemiological and Longitudinal Studies

Epidemiological and Longitudinal Studies

In 2008, the world's most comprehensive and longest running longitudinal examination of human aging celebrated an astonishing 50 years of groundbreaking research that has transformed the field of geriatrics. Since its establishment in 1958, the NIH-supported Baltimore Longitudinal Study of Aging (BLSA) has provided a wealth of information on the physical consequences of aging and has helped distinguish changes due to aging from those due to disease. For example, BLSA scientists have elucidated the relationship between age-related changes in the arteries and cardiovascular disease and also have distinguished normal age-related declines in cognitive ability from those associated with Alzheimer's disease and related conditions. In 2009, BLSA launched a new initiative called IDEAL (Insight into the Determinants of Exceptional Aging and Longevity), which will study people 80 years of age and older who are living free of physical and cognitive disease. This effort will help identify the genetic, environmental, social, and behavioral factors that allow some individuals to enjoy excellent health well into their 80s while others experience disease and physical decline earlier in life.

Introduction

Epidemiological studies examine factors that contribute to health and disease in human populations using a broad range of approaches. Persons or groups can be followed over time in longitudinal studies, or a snapshot of information can be collected at a single point in time. Studies can be done retrospectively, examining outcomes that have already occurred and factors that may have contributed to health or disease, or they can be done prospectively by beginning to monitor a population of interest before a particular disease-related outcome occurs. Many epidemiological studies are observational in nature, collecting information about and comparing groups—called cohorts—made up of individuals who share a characteristic of interest (e.g., tobacco use, age, educational status). Population studies are another type of epidemiological research, aimed at providing a better understanding of populations—how they change in size, composition, and distribution; the complex social, economic, and cultural factors that cause such changes; and the consequences of population change for health and well-being at the individual and societal levels.

Epidemiological research is a critical part of the activities undertaken to fulfill the NIH mission of pursuing fundamental knowledge of living systems and applying that knowledge to extend healthy life and reduce the burdens of illness and disability. Epidemiological research is important for investigating all types of disease and draws on expertise from a wide range of disciplines; thus, it is not surprising that virtually all NIH ICs are involved with epidemiological research in some capacity. As part of the continuum from basic to applied research, epidemiological and longitudinal studies often test the findings of laboratory or clinical research at the population level. For example, animal studies demonstrating the reproductive and neurological effects of bisphenol A (BPA)—a common component of plastics—have prompted large-scale epidemiological studies to ascertain the exposure and health effects of this chemical in humans. Additionally, observations made through epidemiological studies often result in the formulation of new or modified hypotheses that spur new basic, translational, and clinical studies. For example, epidemiological studies in the 1950s showing that tobacco smoking increases risk of lung cancer led to extensive research to identify the carcinogens and mechanisms involved in tobacco-related carcinogenesis. Thus, epidemiological and longitudinal studies are essential for linking bench to bedside to population.

Animal studies demonstrating the reproductive and neurological effects of bisphenol A (BPA)—a common component of plastics—have prompted large-scale epidemiological studies to ascertain the exposure and health effects of this chemical in humans.

The population-based perspective provided by epidemiological studies often helps to form a foundation for the practical application of scientific knowledge, such as changes in clinical practice and the development of public policy. For example, the Framingham Heart Study, which was initiated in 1948, linked risk of cardiovascular disease, which was rapidly becoming a major public health concern by the middle of the 20th century, to factors such as high serum cholesterol levels, hypertension, and cigarette smoking. Based on these results, clinicians were better able to identify

patients at high risk for cardiovascular disease. More recently, a series of NIH studies revealed an increased risk of cancer following exposure to benzene at levels below 10 parts per million and documented blood toxicity following exposure levels of under 1 part per million.^{1,2} These data were used by the U.S. Environmental Protection Agency (EPA) as it developed a new rule in 2007 that limits the benzene content in gasoline and adopts new standards for passenger vehicles and portable fuel containers to limit emissions of benzene and other hazardous air pollutants.³

Many of the NIH-supported epidemiological studies described in this section will inform future clinical practice guidelines and public policy, although it sometimes takes decades for the fruits of these large-scale, long-term studies to be realized. As the Nation's leading Federal agency for biomedical research, NIH is well suited to conduct these sorts of studies. Its stable infrastructure allows it to invest in the types of decades-long projects that are particularly informative for studying factors that contribute to disease development. Furthermore, NIH fosters team science among and between intramural and extramural scientists with diverse expertise, facilitating multidisciplinary studies that lead to a comprehensive understanding of health and disease.

Catalog of Epidemiological & Longitudinal Research Activities

Currently, NIH does not collect the information necessary for a catalog of epidemiological studies and longitudinal studies. This capacity is expected to be developed in the future for integration with RCDC.

Summary of NIH Activities

Although not comprehensive, the following summary highlights several ongoing NIH-supported epidemiological and longitudinal studies. These examples illustrate the strengths of NIH's epidemiological research portfolio: continuing efforts to make the most of past investments, an appreciation of the myriad factors that contribute to health and disease, and cooperation within and beyond the biomedical research community to achieve outcomes relevant to public health.

Investments in the Past Continue to Pay Off

NIH has been investing in epidemiological and longitudinal studies for most of its history. Some of these studies have been ongoing for decades. For example, the Framingham Heart Study has been running for more than 60 years. The infrastructure created and data collected from these studies continue to advance understanding of disease and health in new and exciting ways. Prolonged follow up also has enormously increased the value of these studies, and their existence helps form the foundation for extraordinary opportunities in biomedical research today.

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Continuing to Follow Existing Cohorts

It has become clear that many of the factors contributing to health and disease are present and begin to exert their influence long before clinical presentation of a problem. NIH-supported longitudinal studies of many cohorts conducted over the past several decades are continuing to elucidate how diverse factors integrate and interact to contribute to disease over time as well as answering new research questions. The National Longitudinal Study of Adolescent Health (Add Health) is one example. It was established as a joint effort of 18 NIH Institutes and other Federal offices to examine how families, peers, schools, and neighborhoods influence the health-related behaviors of teens and their use of health care. During the first wave of the study in 1994-1995, information was collected through administration of more than 90,000 surveys to students in grades 7 through 12 and 20,000 at-home interviews with students and their parents. Follow up was conducted with the adolescents 1 year later and again in 2001-2002. Another round of follow up with the original Add Health cohort, now 24 to 32 years of age, was initiated in 2008. The social, behavioral, environmental, and biological data collected through this wave of the study will provide insight into developmental and health trajectories as adolescents

Epidemiological and Longitudinal Studies

move into young adulthood and assume adult roles and responsibilities. For example, one recent analysis revealed that individuals who married or moved in with a partner were more likely to become obese than those who were dating, suggesting that interventions targeted at those establishing a shared household may be useful.⁴ More than 600 publications have been generated based on Add Health data, which continue to be available for both scientific study and policy analyses.

The social, behavioral, environmental, and biological data collected through the National Longitudinal Study of Adolescent Health (Add Health) study will provide insight into developmental and health trajectories as adolescents move into young adulthood and assume adult roles and responsibilities.

Using Specimens from Existing Cohorts to Identify Genetic Markers of Disease

In addition to following cohorts for extended periods of time, NIH is leveraging its past and current investments in population-based studies to study the genetic basis of disease. The Cancer Genetic Markers of Susceptibility (CGEMS) project has conducted genome-wide association studies (GWAS) to identify genetic variants associated with risk of prostate and breast cancer using specimens from 11 existing cohorts. CGEMS researchers have identified new genetic variants in two regions of DNA (located on chromosomes 1 and 14) that may be associated with risk of sporadic breast cancer, as well as regions of chromosomes 7, 8, 10, and 11 that are associated with moderate increases in the risk of prostate cancer.^{5, 6, 7} The same region on chromosome 8 also may be involved in colon cancer and certain other tumors, suggesting a novel pathway of cancer susceptibility shared by a variety of cancers.

The Cancer Genetic Markers of Susceptibility project has identified genetic variants associated with breast and prostate cancer, as well as a chromosomal region of shared susceptibility for several other cancers.

Another NIH initiative called the SHARe (SNP Health Association Resource) project also is conducting GWAS on several large cohorts to elucidate genetic contributors to disease. One of the cohorts being examined as part of SHARe is that of the Framingham Heart Study. The Framingham cohort was first established in 1948 and has since been expanded to include the children and grandchildren of the original participants. As part of SHARe, the DNA of more than 9,000 Framingham participants from all three generations has been analyzed. These genetic data, along with information about major disease risk factors (e.g., systolic blood pressure, cholesterol levels, cigarette use), have been added to dbGaP (the database of Genotypes and Phenotypes) and are available for use by researchers interested in investigating genetic contributors to disease.

Gaining Insights for Policy from Long-Term Population-Based Studies

Long-term NIH studies also have been used to inform the decisions of policymakers and assess the short- and long-term effects of policies on health or health-related behaviors. In 1975, NIH launched Monitoring the Future (MTF), a study that tracks the beliefs, attitudes, and behaviors of adolescents and young adults. MTF surveys approximately 50,000 students in grades 8, 10, and 12 each year. In addition, follow up is conducted with a subset of each graduating class until they reach age 30. Among other things, MTF gathers information on alcohol and other drug use, allowing identification of emerging substance abuse trends as well as factors contributing to them. MTF data have informed policy discussions on substance abuse and have been used by the White House Office of National Drug Control Policy to monitor progress toward national health goals. The most recent MTF survey, conducted in 2008, found that the rate of cigarette smoking was the lowest it has been in the 33-year history of the survey. The survey also revealed a 25 percent decline since 2001 in student reports of illicit drug use in the past month. However, after exhibiting consistent declines since the mid-1990s, marijuana use appears to have leveled off. Moreover, prescription drugs are now among those most commonly abused by high school seniors, following marijuana, alcohol, and tobacco.⁸

In 2008, the Monitoring the Future study found that the rate of cigarette smoking among students in grades 8, 10, and 12 was the lowest it has been in the 33-year history of the survey.

The increasing age of the U.S. population has major implications for policy. The NIH Health and Retirement Study (HRS) collects multidisciplinary data about the physical and mental health, insurance coverage, financial situations, family support systems, work status, and retirement planning of Americans over age 50 to help inform policy decisions. Now in its 16th year, HRS surveys more than 22,000 Americans every 2 years. Nearly 1,000 researchers have used HRS data to publish more than 1,000 reports, including more than 600 peer-reviewed journal articles and book chapters, and 70 doctoral dissertations.⁹ Recently, HRS data were used to measure health insurance coverage trends as people approach and pass the age of eligibility for Medicare. The analysis found differential results for particular populations. For example, people who were unmarried or individuals in particularly good or poor health had an increased likelihood of being uninsured prior to becoming eligible for Medicare. Individuals in good health may have believed they did not need insurance while those in poor health may not have been able to obtain coverage. Nonwhites and those in good health had an increased likelihood of having Medicare-only coverage after reaching the age of eligibility for Medicare.¹⁰

Pursuit of a Comprehensive Understanding of Health and Disease

A comprehensive understanding of health and disease requires consideration of factors from the molecular to the community level. Integration of this information necessitates a systems approach that takes into account genetics, biology, and the social sciences. Conducting studies in diverse contexts helps to elucidate how these contributors converge to influence health and also ensures that insights gained will benefit different populations. NIH supports a number of studies in the United States and worldwide aimed at building a comprehensive understanding of disease and health with the goal of identifying new and more effective approaches for prevention and treatment.

Determining How Genes and Environment Interact to Influence Disease Risk

With the availability of high-throughput sequencing technology and the completion of the Human Genome Project, research on the genetic basis of disease has exploded over the past 2 decades. More recently, it has become clear that environmental factors can have a strong influence on how genetic background affects disease risk. To facilitate research on the interactions of genes and the environment, NIH has launched a large volunteer DNA-banking project called the Environmental Polymorphism Registry (EPR). The goal of the EPR is to collect DNA samples from 20,000 individuals to allow scientists to study how genes contribute to diseases such as diabetes, heart disease, cancer, asthma, and many others. The study participants are in the greater Research Triangle Park region of North Carolina, which has a diverse population in terms of age, ethnicity, economic and educational background, and health status. Unlike anonymous DNA registries, researchers using EPR are able to identify and contact registry participants—with their consent—for further study if they are found to have potentially significant genetic variants. Another unique feature of the EPR is that two distinct populations are solicited for participation: an apparently healthy population as well as a population recruited from various clinics and hospitals in the area. Individuals in the clinic population have an array of medical conditions; their inclusion in the EPR increases the likelihood of identifying subjects with both the genetic and clinical characteristics of interest. These aspects of the EPR give scientists the flexibility to design follow-up studies while reducing biases that can occur in genetic epidemiology studies when subjects are recruited based primarily on their observable clinical or physical traits. Although many genes will be studied as part of the EPR, the focus will be on so-called "environmental response genes" that increase or decrease disease risk when combined with an environmental exposure.

The Environmental Polymorphism Registry will collect DNA from 20,000 people to allow scientists to study how genes contribute to diseases such as diabetes, heart disease, cancer, asthma, and many others.

Through the Breast Cancer and the Environment Research Centers (BCERC), NIH is studying how interactions of chemical, physical, and social factors, combined with genetic factors, affect breast development during puberty and breast

Epidemiological and Longitudinal Studies

cancer predisposition. An epidemiologic study being conducted as part of BCERC is prospectively following through puberty a cohort of multiethnic 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet influences fat tissue and alters the effects of hormones on sexual maturation. Endocrine disruptors, irradiation, and psychosocial elements also will be studied for effects. The BCERC directly relates to one of NIH's Government Performance and Results Act (GPRA) goals: By 2011, conduct studies of girls aged 6 through 8 years to determine the associations of 12 environmental exposures with age of onset of puberty and progression through puberty (SRO-5.10).

Improving Treatment and Prevention

In addition to providing a more complete picture of disease, multidisciplinary involvement is crucial for generating results with practical implications for clinical practice or behavior. Several ongoing NIH studies have the potential to alter clinical practice to improve health and minimize the burden of disease. The Oral HIV/AIDS Research Alliance (OHARA) is part of the AIDS Clinical Trials Group, the world's largest HIV clinical trials organization. OHARA drives and supports studies in the United States and internationally to improve diagnosis, treatment, and management of AIDS-related oral complications. These complications—which include ulcers and tumors, fungal infections, and painful viral lesions—occur in nearly all of the 33 million HIV-infected people worldwide and can compromise nutrition and exacerbate immune suppression. Although antiretroviral therapy alleviates some of the symptoms, many oral lesions require additional specific treatment. NIH provides central management and leadership for OHARA researchers, which include experts in epidemiology, mycology, and virology.

Through the COPDGene study, NIH is performing genetic testing in more than 10,000 current or former smokers to identify genetic characteristics associated with the presence of chronic obstructive pulmonary disease (COPD). This research should help reveal why some smokers develop serious lung disease while others do not. In addition to helping clinicians identify smokers at high risk for COPD, the study results likely will reveal molecular pathways involved in the pathogenesis of the disease that may be targets for prevention or therapy.

Identifying Disease Risk among Diverse Populations

Research has shown that factors such as genetic background, geographic location, socioeconomic status, and cultural traits can result in variations in disease risk among different populations. This observation has important implications for biomedical research, as results in one population may not necessarily apply to another. Thus, it is important to include study participants with diverse backgrounds and characteristics to increase the likelihood that insights gained through study findings will benefit all groups of people. In this regard, NIH is supporting the Multi-Ethnic Study of Atherosclerosis (MESA), a multicenter epidemiological study of cardiovascular disease in men and women from four ethnic groups—white, African American, Hispanic, and Chinese. This study, which began in 1999, has measured and compared the value of chest computed tomography (CT), cardiac magnetic resonance imaging, carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for predicting the development of cardiovascular disease. In one recent study, researchers used MESA data to confirm that CT measurements of coronary calcium, previously shown to predict coronary heart disease among white populations, are effective predictors in African Americans, Hispanics, and Chinese as well.¹¹ Clinical and genomic data from the MESA cohort will be made available to the research community through SHARe to facilitate GWAS.

The Multi-Ethnic Study of Atherosclerosis is studying cardiovascular disease in white, African American, Hispanic, and Chinese populations.

Culture of Cooperation to Promote Public Health

Bridging the gap between research and application requires the contributions of numerous scientists with diverse expertise. NIH therefore fosters a culture of cooperation, encouraging researchers to build teams capable of designing and conducting research with identified potential to improve public health.

Teaming Up to Improve the Study of Disease

Recognizing the need for large-scale collaborations to study the role of gene-gene and gene-environment interactions in the etiology of cancer, NIH formed the Cohort Consortium. The mission of the Consortium—which currently comprises 37 cohorts and more than 4 million individuals—is to foster communication among investigators leading cohort studies of cancer; promote collaborative projects for topics not easily addressed in a single study; and identify common challenges in cohort research and search for solutions. Investigators team up to use common protocols and methods to facilitate parallel and pooled analyses of data. In addition to the CGEMS initiative (described above), another project of the Cohort Consortium is the Pancreatic Cancer Cohort Consortium in which investigators from 12 prospective epidemiologic cohort studies and 1 case-control study are collaborating to carry out whole-genome scans of common genetic variants to identify markers of susceptibility to pancreatic cancer.

Bringing Together NIH Institutes and Centers

The 27 NIH ICs collectively house expertise on a broad spectrum of diseases, populations, and research support methods. Large-scale epidemiological studies provide an ideal opportunity for researchers from the various NIH components to come together to conduct innovative studies on the diverse factors that coalesce to influence public health and disease. One example of collaboration among NIH ICs is the Hispanic Community Health Study, which is sponsored by six NIH Institutes (NHLBI, NCMHD, NIDCD, NIDCR, NIDDK, and NINDS) and the NIH Office of Dietary Supplements. This multicenter study aims to recruit 16,000 persons of Hispanic/Latino descent, with a focus on individuals with Cuban, Puerto Rican, Mexican, and Central/South American ancestry. Participants will undergo a series of physical examinations and interviews to identify factors that influence a wide variety of diseases, disorders, and conditions, including heart disease, asthma, sleep disorders, diabetes, cognitive impairment, and more. Particular attention will be given to the role of cultural adaptation and disparities in the prevalence and development of disease. The insights gained from this study will be invaluable because the U.S. Hispanic population, already the largest minority population in the country, is expected to triple by 2050.

The Hispanic Community Health Study will provide insight into the prevalence of and risk factors for a variety of diseases within the most rapidly growing ethnic population in the United States.

Collaborating with Other Federal Departments and Agencies

As the Nation's premiere biomedical research agency, NIH seizes the opportunity to collaborate with other Federal departments and agencies on projects related to health. One example of such an intergovernmental collaboration is the Agricultural Health Study (AHS), cosponsored by two NIH Institutes and EPA. With a cohort of more than 89,000 private and commercial pesticide applicators and their spouses, the study is exploring occupational, lifestyle, and genetic factors that may affect the rate of diseases in farming populations. Although current medical research suggests that agricultural workers are healthier overall than the general U.S. population, they may have higher rates of some types of cancer and other conditions like asthma, neurologic disease, and reproductive problems. A recent AHS study found that elevated exposure to certain pesticides was associated with a doubling of the risk of adult-onset asthma.¹² Another study evaluated the relationship between lifetime exposure to pesticides and diabetes; of the 50 pesticides evaluated, 7 were associated with an increased risk of diabetes. The strongest association was with the organophosphate insecticide trichlorfon.¹³ Continuing identification of links between agricultural exposures and health problems will inform future policies designed to protect farmers, their families, and others who live or work in agricultural areas.

Epidemiological and Longitudinal Studies

The Agricultural Health Study has linked exposure to certain pesticides to elevated risk of diabetes and adult-onset asthma.

NIH also is working with the U.S. Army to evaluate soldiers across all phases of Army service (e.g., predeployment training, deployment and noncombat assignments, and post-separation re-integration to civilian life) as part of the Collaborative Study of Suicidality and Mental Health in the U.S. Army. This study was prompted by growing concern over the high rates of mental health and behavioral adjustment problems, including substance abuse and addiction, among recent U.S. military combat veterans and increasing rates of suicide among soldiers. The goal of the study is to identify modifiable risk and protective factors for, as well as moderators of, suicide-related behaviors. In a separate effort, three NIH Institutes, in conjunction with the Department of Veterans Affairs, have issued a call for studies examining how trauma, stress, and substance use/abuse emerge in U.S. military personnel, veterans, and their families, with a focus on how these disorders can be prevented and treated. NIH also is launching a study of the impact of existing national, state, and/or local community-based programs that are addressing the re-entry/adjustment and mental health needs of recent combat veterans. This initiative will inform strategic approaches to fostering the successful transition of all service members to civilian roles.

Conclusion

Epidemiological and longitudinal studies are essential to NIH's efforts to bridge the results of basic, translational, and clinical studies to practical applications such as clinical practice and public policy. Many NIH epidemiological and longitudinal studies have had substantial influence on public health, with current investments likely to follow suit. This success is due to a number of factors, including investment in long-term studies, pursuit of a comprehensive view of disease, and promotion of a culture of cooperation.

The studies described above represent only a fraction of NIH's efforts in this area. Epidemiological studies are being carried out by experts in a number of disciplines, including, but not limited to, epidemiology, behavioral and social sciences, genetics, molecular biology, public health, economics, statistics, and data management. Although still far from comprehensive, additional notable examples of NIH-supported epidemiological and longitudinal studies, as well as further information about some of the activities mentioned above, are found on the following pages.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research

I = Supported through **I**ntramural research

O = **O**ther (e.g., policy, planning, or communication)

COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program

GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct

ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Investments in the Past Continue to Pay Off

Population Research: Given the Nation's increasing diversity and changing demographics, it is critical to understand how trends in such areas as immigration, fertility, marriage patterns, and family formation affect the well-being of children and families. NIH research in these areas allows policymakers and program planners to better address public health needs. For instance:

- The Fragile Families and Child Well-Being Study follows children born to unmarried parents to assess how economic resources, father involvement, and parenting practices affect children's development.
- The New Immigrant Survey follows the first nationally representative sample of legal immigrants to the United States, providing accurate data on legal immigrants' employment, lifestyles, health, and schooling before and after entering the country.
- Several NIH Institutes are supporting The National Longitudinal Study of Adolescent Health, which integrates biomedical, behavioral, and social science data to discover the pathways that lead to health and/or disease in adulthood.

→ For more information, see <http://www.cpc.unc.edu/addhealth/>

→ For more information, see <http://nis.princeton.edu/index.html>

→ For more information, see <http://www.fragilefamilies.princeton.edu/index.asp>

→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*

→ (E) (NICHD, NCI, NCMHD, NIA, NIAAA, NIAID, NIDA, NIDCD, NINR, OAR, OBSSR, ORWH)

Genome-Wide Association Studies of Cancer Risk: The Cancer Genetic Markers of Susceptibility (CGEMS) project is a signature initiative that uses genome-wide association studies (GWAS) to identify genetic variants and mechanisms associated with cancer risk. Understanding these variants and mechanisms may lead to new preventive, diagnostic, and therapeutic interventions. CGEMS investigators have pinpointed genetic variants associated with elevated prostate cancer risk as well as variants associated with increased breast cancer risk. The same genetic variant was shown to be involved in increased prostate, colon, and other cancers, suggesting a common mechanistic pathway for susceptibility to a variety of cancers. Another GWAS project, the Cohort Consortium, is a unique extramural/intramural collaboration that allows Consortium partners to share access to data on 37 cohorts comprised of 4 million people from diverse populations. Each cohort contains extensive information on known or suspected risk factors and biospecimens collected pre- and post-diagnosis. The large number of study subjects permits the detection of modest genetic effects, as well as studies of variants involved in less common cancers. One cohort within the Consortium, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort, includes about 2.9 million specimens. These pre-diagnostic specimens provide a valuable resource for studies of cancer etiology and early detection. Researchers can correlate changes in molecular profiles associated with the onset of different types of disease, thereby providing valuable insights into the actual mechanisms of human carcinogenesis.

→ For more information, see <http://cgems.cancer.gov>

→ For more information, see <http://epi.grants.cancer.gov/Consortia/cohort.html>

→ For more information, see <http://www.parplco.org>

→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Genomics*

→ (E/I) (NCI)

A Look at Drug Abuse Trends: Local to International: Two major systems of data collection are helping to identify substance abuse trends locally, nationally, and internationally: Monitoring the Future Survey (MTF) and the Community Epidemiology Work Group (CEWG). Both help to surface emerging drug abuse trends among adolescents and other populations, and guide responsive national and global prevention efforts. The MTF project, begun in 1975, has many purposes, the primary one being to track trends in substance use, attitudes, and beliefs among adolescents and young adults. The survey findings also have been used by the President's Office of National Drug Control Policy to monitor progress toward national health goals. The MTF project includes both cross-sectional and longitudinal formats—the former given annually to 8th, 10th, and 12th graders to see how answers change over time, and the latter given every 2 years (until age 30), then every 5 years to follow up on a randomly selected sample from each senior class. CEWG, established in 1976, provides both national and international information about drug abuse trends through a network of researchers from different geographic areas. Regular meetings feature presentations on selected topics, as well as those offering international perspectives on drug abuse patterns and trends. CEWG findings reported in 2008 and 2009

Epidemiological and Longitudinal Studies

show decreases in methamphetamine indicators (e.g., treatment admissions), suggesting that the problems that had escalated in the first half of the decade may have stabilized or declined. Development of a Latin American Epidemiology Network is underway. NIH also has provided technical consultation for the planning and establishment of an Asian multicity epidemiological network on drug abuse.

- For more information, see <http://www.monitoringthefuture.org/>
- For more information, see <http://www.drugabuse.gov/about/organization/CEWG/CEWGHome.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E) (NIDA)

Advances in Minority Mental Health Research: Results from NIH's Collaborative Psychiatric Epidemiology Surveys (CPES) have continued to shed light on the risk, prevalence, and outcomes associated with mental disorders in minority populations. Two CPES surveys, the National Latino and Asian American Study (NLAAS), and the National Survey of American Life (NSAL), are large, nationally representative epidemiologic surveys that focus, respectively, on the mental health epidemiology of Latinos and Asians, and African Americans. Examples of important research that has emerged from the CPES include an FY 2009 study from the NSAL that found that African American teens, especially girls, are at increased risk for suicide attempts, even if they have not been diagnosed with a mental disorder. The study's findings may be used to improve clinicians' screenings for suicidal behavior among adolescent African Americans. Additionally, an FY 2009 study using data from the NLAAS and the National Co-morbidity Survey Replication found that previous research showing native-born Latinos to be at higher risk for mental disorders than nonnative-born Latinos may not be true across all Latino subgroups. NLAAS researchers found that this widely reported phenomenon (the "immigrant paradox") was true in some subgroups, but it did not hold in others (e.g., among Puerto Ricans). The results emphasize the heterogeneity of the Latino population and suggest the importance of addressing this population's subgroups in future research.

- Joe S, et al. *J Am Acad Child Adolesc Psychiatry* 2009;48(3):271-82. PMID: 19182692. PMCID: PMC2760075.
- Alegria M, et al. *Am J Psychiatry* 2008;165(3):359-69. PMID: 18245178. PMCID: PMC2712949.
- For more information, see <http://www.nimh.nih.gov/science-news/2009/black-teens-especially-girls-at-high-risk-for-suicide-attempts.shtml>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NIMH)

Demographic and Economic Studies of Aging: NIH supports a number of studies on the demographic and economic changes in our society. The Health and Retirement Study (HRS) is the leading source of combined data on health and financial circumstances of Americans over age 50 and a valuable resource to follow and predict trends and help inform policies for an aging America. Now in its 16th year, the HRS follows more than 20,000 people at 2-year intervals and provides researchers with an invaluable and growing body of multidisciplinary data on the physical and mental health of older Americans, insurance coverage, finances, family support systems, work status, and retirement planning. Recently, researchers used HRS data on memory and judgment of a large subset of HRS participants to determine trends in cognitive status of those age 70 and older. The researchers found that cognitive impairment dropped from 12.2 percent in 1993 to 8.7 percent in 2002. The study recently has been expanded to include additional key constructs in cognitive aging. NIH also has renewed its program of Centers on the Demography and Economics of Aging to foster research in the demography, economics, and epidemiology of aging and to promote the use of important datasets in the field. The achievements of this program in past years were recognized in September 2008 by the Heidelberg Award for Significant Contributions to the Field of Gerontology, a triennial international competition.

- For more information, see <http://hrsonline.isr.umich.edu>
- For more information, see <http://agingcenters.org>

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIA)

Database of Genotype and Phenotype (dbGaP): Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics, and other scientific data, NIH established dbGaP to house the results of genome-wide association studies (GWAS), which examine genetic data of de-identified subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2009, dbGaP included results from more than 40 GWAS, including genetic analyses related to such diseases as Parkinson's disease, ALS, diabetes, alcoholism, lung cancer, and Alzheimer's disease. dbGaP is the central repository for many NIH-funded GWAS to provide for rapid and widespread distribution of such data to researchers and accelerate the understanding of how genes affect the susceptibility to and severity of disease.

- For more information, see <http://view.ncbi.nlm.nih.gov/dbgap>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (NLM)

Epidemiologic Studies of Osteoporosis: NIH supports several prospective cohort studies, including the Study of Osteoporotic Fractures (SOF) in women and Mr. OS, a study of osteoporosis and other age-related diseases in men. The studies, which have been underway since 1986 and 1999, respectively, identified characteristics associated with fracture risk in older Americans. Assessing risk is important because the devastating consequences of low bone mass can be prevented. For example, simple changes to a person's home (e.g., adding more lights, removing clutter) can prevent falls. A balanced diet and modest exercise build bone strength, and medications can slow disease progression. SOF, Mr. OS, and other studies are providing information about osteoporosis diagnosis, treatment, and prevention. SOF and Mr. OS reinforced a notion, outlined in the Surgeon General's 2004 report on Bone Health and Osteoporosis, that older people who have a fracture should be tested for osteoporosis—even if the fracture occurred because of a traumatic injury (e.g., a fall off a ladder or an auto accident) that could hurt a healthy young person. Mr. OS is generating data that the U.S. Preventive Services Task Force can incorporate into guidance on using bone mineral density to assess fracture risk. Scientists using data from the Framingham Osteoporosis Study recently reported that men and women who consumed the most vitamin C had fewer hip fractures than those who consumed less vitamin C—a finding that may have implications for the recommended intakes established for vitamin C. Women's Health Initiative investigators demonstrated that low blood levels of vitamin D, which helps the body absorb calcium from food, also is associated with hip fracture risk.

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- Sahni S, et al. *Osteoporos Int* 2009;20(11):1853-61. PMID: 19347239. PMCID: PMC2766028.
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/11_28.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/low_vitD_hip_fracture.asp
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIAMS, NCR, NHLBI, NIA)

Epidemiological and Longitudinal Studies

Pursuit of a Comprehensive Understanding of Health and Disease

Environmental Polymorphisms Registry: NIH, in collaboration with the University of North Carolina's General Clinical Research Center, has launched a large volunteer DNA banking project named the Environmental Polymorphisms Registry (EPR). The goal of the EPR is to collect DNA samples from 20,000 individuals in the greater Research Triangle Park region of North Carolina through local health care systems, study drives, health fairs, and other means. This area has a diverse population varying in age, ethnicity, economic and educational backgrounds, and health status. The EPR offers a valuable resource for human genomic studies, especially when compared to anonymous DNA registries. It was designed for scientists to screen for functionally significant alleles and to identify subpopulations of individuals with shared genotypes, and then correlate their genotypes with their phenotypes in a process known as "recruit-by-genotype." The value of the EPR lies in the ability to identify and then re-contact subjects with potentially significant polymorphisms for further study. A unique feature of the EPR is that two distinct populations are solicited, an apparently healthy population recruited from the general population as well as a clinic population recruited from various clinics and hospitals in the area. Individuals in the clinic population have a wide array of medical conditions, and their inclusion in the EPR increases the likelihood of identifying subjects with both the genotypes and phenotypes of interest. These aspects of the EPR give scientists more flexibility in designing follow-up studies while reducing the ascertainment bias that can occur in genetic epidemiology studies when subjects are recruited based on phenotype.

- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (NIEHS)

Understanding HIV, TB, and Malaria Co-infection: Tuberculosis (TB) is one of the leading causes of death among people living with HIV/AIDS and one of the most common opportunistic infections they experience. HIV and TB reinforce one another: HIV activates dormant TB in a person, who then becomes infectious and able to spread the TB bacillus to others. HIV infection increases the risk of getting TB by a factor of 20 or more, according to the World Health Organization. Similarly, many HIV-positive individuals are co-infected with malaria and face poorer treatment outcomes for both diseases. Notably, malaria infection in pregnant HIV-positive patients leads to worse outcomes for both the mother and the child. NIH is increasing its focus on TB co-infection with HIV, malaria, and other pathogens. Questions addressed include when to start antiretroviral therapy (ART) in patients co-infected with HIV and TB and how best to prevent development of active TB disease in HIV-infected individuals who are receiving ART. Other studies attempt to develop new diagnostics and TB treatments for individuals co-infected with TB and HIV. In addition, several studies underway assess how best to treat women and children with HIV and either TB or malaria. Finally, the Children with HIV and Malaria Project, a prospective, longitudinal study of Ugandan children, is designed to determine if HIV increases the risk of malaria in children, whether malaria is associated with accelerated HIV disease progression, if malaria treatment has a higher failure rate in HIV-infected children in comparison with HIV-uninfected children, and whether trimethoprim-sulfamethoxazole prophylaxis increases incidence of resistant malaria. The study enrolled 300 children with more than 3 years of follow-up, and concluded in September 2009.

- For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/therapeutics/intro/drug_discovery.htm
- For more information, see <http://www3.niaid.nih.gov/topics/tuberculosis/>
- For more information, see <http://www.who.int/entity/tb/challenges/hiv/tbhivbrochure.pdf>
- For more information, see <http://www.unaids.org/en/policyandpractice/hivtreatment/coinfection/tb/default.asp>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIAID)

The Sister Study: Environmental Risk Factors for Breast Cancer: The NIH Sister Study prospectively examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The frequency of relevant genes and shared risk factors is greater among sisters, increasing the ability of the study to detect risks. Researchers will collect data on potential risk factors and current health status, and will collect and bank blood, urine, and environmental samples for future use in studies of women who develop breast cancer or other diseases compared with those who do not. Analysis of new cases will assess the separate and combined effects of environmental exposures and genetic variations that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors like smoking, occupational exposures, alcohol, diet and obesity, and include analysis of phthalates, phytoestrogens, metals, insulin, growth factors, vitamins and nutrients, and genes in blood and urine. The study also allows investigators to examine a wide range of health outcomes of relevance to women, and to create a framework from which to test new hypotheses as they emerge. In addition to its focus on genetic and environmental causes of breast cancer, the prospective Sister Study tracks changes in health status over time. Among the chronic diseases currently studied are uterine fibroids and endometriosis, rheumatoid arthritis and other autoimmune diseases, thyroid disease, asthma, and cardiovascular diseases. As the cohort ages, the Sister Study will address aging-related health outcomes including osteoporosis, Parkinson's disease, and age-related cognitive decline.

- For more information, see <http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm>
- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Minority Health and Health Disparities*
- (E/I) (NIEHS, NCMHD)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects adipose tissue and alters hormonal control of sexual maturation. Endocrine disruptors, irradiation, and psychosocial elements also will be studied for effects.

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- Kouros-Mehr H, et al. *Curr Opin Cell Biol* 2008;20(2):164-70. PMID: 18358709. PMCID: PMC2397451.
- Ewald AJ, et al. *Dev Cell* 2008;14(4):570-81. PMID: 18410732. PMCID: PMC2773823.
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- Egeblad M, et al. *Dis Model Mech* 2008;1(2-3):155-67; discussion 165. PMID: 19048079. PMCID: PMC2562195.

Epidemiological and Longitudinal Studies

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→ For more information, see <http://www.bccrc.org/>

→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*

→ (E) (NIEHS, NCI) (GPRA)

Cancer Epidemiology Biomarkers and Prevention: The long-term Sister Study looks at the environmental and genetic characteristics of women whose sisters have had breast cancer to identify factors associated with developing breast cancer. A pilot study that was part of the Sister Study shows that women who maintain a healthy weight and who have lower perceived stress may be less likely to have chromosome changes associated with aging than obese and stressed women. Recently, NIH funded a study looking at 94 women whose breast cancer had spread or returned. Researchers asked the women whether they had ever experienced stressful or traumatic life events. The categories ranged from traumatic stress to some stress to no significant stress. The comparison revealed a significantly longer disease-free interval among women reporting no traumatic or stressful life events.

→ For more information, see <http://www.niehs.nih.gov/news/releases/2009/sister-study.cfm>

→ For more information, see

<http://www.nlm.nih.gov/medlineplus/magazine/issues/winter08/articles/winter08pg6b.html>

→ This example also appears in Chapter 2: *Cancer*

→ (E/I) (NCI, NIA)

OHARA: The Oral HIV/AIDS Research Alliance: At the vanguard of basic, translational, and clinical research to combat the oral manifestations of HIV/AIDS is the NIH-funded Oral HIV/AIDS Research Alliance (OHARA), which drives and supports novel clinical studies in the United States and internationally to improve diagnosis, treatment, and management of comorbidities of AIDS-related oral complications, including necrotizing ulcers and tumors, fulminating fungal infections, and painful viral lesions that occur in almost all 33 million people infected worldwide. Their devastating effects compromise nutrition and exacerbate immune suppression in addition to the local effects. Even since the advent of antiretroviral therapy (ART), oral complications of AIDS remain a major public health problem. Though ART alleviates some symptoms, many oral lesions need additional specific treatment and globally, only 30 percent of HIV-infected individuals for whom ART is indicated receive it. The estimated prevalence of U.S cases of HIV/AIDS in 2006 exceeded 1.1 million, while about 56,300 people were newly infected with HIV that year. In its fourth year OHARA is making significant strides for people living with HIV/AIDS. OHARA is formed by world-expert scientists and clinicians. Its success is driven by three geographically and academically separate core units that provide expertise in epidemiology, mycology, and virology, embraced by a centralized NIH management and leadership. Currently, OHARA has ramped up eight clinical studies in various phases. They include studies to assess the clinical effectiveness of diagnostic tools for

HIV/AIDS-related conditions, and compare the safety and efficacy of novel treatments and preventive strategies for HIV/AIDS-related oral diseases and malignancies.

- Shiboski CH, et al. *J Oral Pathol Med* 2009;38(6):481-8. PMID: 19594839.
- Jacobson MA, et al. *PLoS One* 2009;4(4):e5277. PMID: 19381272. PMCID: PMC2667217.
- For more information, see <http://aactg.org/committees/scientific/optimization-co-infection-and-co-morbidity-management/subcommittees/ohara-sub-3>
- For more information, see <http://www.nidcr.nih.gov/Research/DER/IntegrativeBiologyAndInfectiousDiseases/AIDSImmuno.htm>
- For more information, see <http://aactg.org/about-actg>
- For more information, see <http://www.who.int/hiv/data/en/>
- For more information, see <http://www.cdc.gov/hiv/topics/surveillance/basic.htm#Main>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
- (E) (NIDCR, NIAID)

The Role of Development in Drug Abuse Vulnerability: NIH supports animal, clinical, and epidemiological research across the lifespan to examine how developmental stage may influence drug abuse vulnerability or protection. The discovery of a protracted period of brain changes during early development and beyond has been critical to understanding the role of brain maturation in decision-making processes and responses to stimuli, including early (e.g., in utero) exposure to drugs. Adolescence has emerged as a particularly vulnerable period, during which an immature brain circuitry can translate into a preponderance of emotional reactivity (vs. higher cognitive control) that gives rise to the impulsive characteristics of many teenagers. This in turn may lead to dangerous risk-taking, such as experimenting with drugs that ultimately can lead to addiction. Using both animal models and clinical research, scientists are beginning to understand how environmental variables can play a key role in shaping brain maturation trajectories. In this regard, imaging, genetic, and epigenetic tools are helping interpret the effects of myriad environmental influences, such as quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics on brain development and behavior. In addition, the field of social neuroscience is harnessing the power of multidisciplinary approaches to tease apart these multilevel phenomena to better understand, for example, the neural mechanisms of peer pressure, the connections between chronic stress and risk of drug abuse initiation, and the impact that different early rearing environments can have on gene expression and behavior.

- For more information, see <http://www.nida.nih.gov/tib/prenatal.html>
- For more information, see <http://www.nida.nih.gov/scienceofaddiction/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDA, NICHD) (GPRA)

Following up on the Multimodal Treatment Study of Children with ADHD (MTA): Children with attention deficit hyperactivity disorder (ADHD), the most common of the psychiatric disorders that appear in childhood, often raise great concern from their parents and teachers because of their inability to focus on or finish tasks. Over time, these children may develop other emotional problems, including mood disorders, loss of self-esteem, and substance abuse. To address these issues, NIH is sponsoring an ongoing, multisite, follow-up of children from the MTA study—a treatment trial of nearly 600 ADHD-diagnosed elementary school children. Findings from the original MTA showed that long-term combination treatment (medication and psychosocial/behavioral treatment), as well as medication-management alone, significantly were superior to intensive behavioral treatments and routine community care in reducing ADHD symptoms. In the follow-up study (n = 485 10 to 13 year olds), children from this cohort and others who received similar pharmacotherapy were assessed for substance abuse outcomes. The study found that despite treatment, children with

Epidemiological and Longitudinal Studies

ADHD showed significantly higher rates of delinquency and substance abuse. Follow-up of the MTA sample is continuing as the participating children go through adolescence and enter adulthood.

- Molina BS, et al. *J Am Acad Child Adolesc Psychiatry* 2009;48(5):484-500. PMID: 19318991.
- For more information, see <http://www.drugabuse.gov/CTN/protocol/0028.html>
- For more information, see <http://www.drugabuse.gov/CTN/protocol/0029.html>
- For more information, see <http://www.nida.nih.gov/ResearchReports/comorbidity/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDA, NIMH)

The Early Childhood Longitudinal Study (ECLS) program: The National Center for Education Statistics, within the Institute of Education Sciences of the U.S. Department of Education, is conducting an ongoing study of a nationally representative sample of children from diverse socioeconomic and racial/ethnic backgrounds who will start kindergarten in 2011. Several Federal agencies, including NIH, are partnering on the study to determine how a variety of home, school, community, and student factors influence the transition of children to school; frame their early school experiences; shape their later school experiences; relate to normal cognitive, social, emotional, and physical child development; and affect academic performance over time. NIH is participating in a field test to work out logistics to determine the feasibility of adding a hearing and vision screening examination in the ECLS. ECLS is the only recent, nationally representative data collection program that enables statistical analysis of relationships between hearing and communication impairments or disorders and subsequent child development from infancy through eighth grade. The intent is to measure the hearing and vision of children during their first year of formal schooling, find out how hearing and vision change as a child grows, establish whether hearing and vision influence other aspects of normal child development, and clarify whether academic performance is influenced by hearing and vision. This information can be used then to evaluate how well early identification and intervention strategies were implemented during the birth cohort years from an earlier ECLS study.

- For more information, see <http://nces.ed.gov/ECLS/>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NEI, NIDCD)

HIV/AIDS Epidemiological and Long-Term Cohort Studies: NIH continues its support of the largest HIV/AIDS observational studies in the United States, the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) of homosexual and bisexual men. These studies repeatedly have made major contributions to our understanding of HIV transmission, disease progression, and best treatment practices. The WIHS, now in its 16th year of research, studies the natural history of HIV infection and AIDS progression in 2,404 HIV-infected and uninfected women, and bridges the gap between theoretic benefits and sustainable gains of antiretroviral therapy. The MACS, now in its 26th year of research, studies the natural history of HIV infection and AIDS progression in 6,973 homosexual and bisexual men at sites located in Baltimore, Chicago, Pittsburgh, and Los Angeles. These domestic cohorts are on the forefront of research to define the clinical manifestations of long-term HIV/AIDS infection. Data from these cohorts have resulted in published studies on the long-term risk of HIV/AIDS on cardiovascular disease. Studies have been initiated on aging, sleep disorders, frailty, renal function, cognitive function, and behavior among HIV-infected persons.

- For more information, see <http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIAID, NCI, NCRR, NICHD, NIDA)

Multicenter AIDS Study (MACS) Small Grant Opportunity: MACS is an ongoing (since 1984) epidemiological study in several U.S. cities of multi-ethnic/racial HIV-infected and HIV-uninfected men who have sex with men (MSM). A

small grant funding opportunity is enhancing the value and potential for new knowledge from the MACS by examining drug use and HIV/AIDS among MSM over the life course. Studies will include an examination of social and behavioral risk factors and trajectories, the role of drug use in neurocognitive function, and other medical consequences. Findings from these studies may lead to new insights and interventions targeting this high-risk group. Such findings reinforce the importance of implementing interventions targeting drug reduction as part of comprehensive and efficacious HIV prevention program.

- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
- (E) (NIAID, NIDA, NIMH)

National Epidemiologic Survey on Alcohol and Related Conditions: Predicting the First Use of Alcohol and Illicit Drugs and Correlated Brain Disorders: The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) collected comprehensive, detailed data from approximately 40,000 individuals on alcohol consumption, use of 10 categories of drugs, and symptoms of alcohol and specific drug use disorders, as well as mood, anxiety, and personality disorders in 2 separate waves. Results from the second wave of this nationally representative survey will provide predictors for the first incidence of substance abuse as well as mood and anxiety disorders. The rates of occurrence at 1 year of the survey were highest for alcohol abuse, alcohol dependence, major depressive disorder, and generalized anxiety disorder. The effects were much greater among men for substance use disorders and greater among women for mood and anxiety disorders, except for bipolar disorders and social phobia. African Americans were at decreased risk for alcohol abuse and Hispanic individuals were at decreased risk of generalized anxiety disorder. Substance abuse, mood disorders, and anxiety disorders occurred at similar or higher rates when compared to lung cancer, stroke, and cardiovascular disease. The higher incidence of all disorders in the youngest individuals highlights the need for increased vigilance in identifying and treating these disorders among young adults.

- Grant BF, et al. *Mol Psychiatry* 2009;14(11):1051-66. PMID: 18427559. PMCID: PMC2766434.
- (I) (NIAAA)

Building a Longitudinal Mental Health Tracking System: NIH has laid the initial groundwork to develop a mental health tracking system that will provide epidemiologic information on mental disorders on a continuing basis. By working with Federal agencies that currently conduct large-scale, ongoing national surveys, and adding detailed measures of mental health status, functioning, and service use, NIH will leverage existing resources to collect important mental health information in a cost-efficient manner. The longitudinal nature of the resulting data will provide NIH the ability to track the prevalence, incidence, severity, correlates, and trajectories of mental disorders, as well as related service use and outcomes, over time. The resulting data also could provide important information on key subgroups (e.g., racial/ethnic populations, people with autism) and geographic areas of varying sizes (e.g., states, counties). These data are critical for targeting future research activities and ensuring the effectiveness of delivered interventions.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIMH)

The National Children's Study (NCS): NCS promises to be one of the richest information resources available for answering questions related to children's health and development and will form the basis of child health guidance, interventions, and policy for generations to come. The landmark study will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. This extensive research effort will examine factors ranging from those in the natural and man-

Epidemiological and Longitudinal Studies

made environment to basic biological, genetic, social, and cultural influences. By studying children through their different phases of growth and development, researchers will be able to understand better the role of these factors in both health and disease. Specifically, the NCS will identify factors underlying conditions ranging from prematurity to developmental disabilities, asthma, autism, obesity and more. The study is led by a consortium of Federal agencies including NIH, CDC, and the EPA.

- For more information, see <http://www.nationalchildrensstudy.gov>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (I) (NICHD, NIEHS)

Fetal Alcohol Effects: The developing embryo and fetus is very vulnerable to the adverse effects of alcohol. Since Fetal Alcohol Syndrome was first recognized around 1970, NIH has supported research on outreach to pregnant women for identification and intervention of risky drinking; research to enhance our ability for early identification of and interventions with prenatal alcohol-affected children; research exploring nutritional and pharmacological agents that could lessen alcohol's adverse effects on the developing embryo/fetus; and research on how alcohol disrupts normal embryonic and fetal development. For example, a recent study with rats showed that choline, an essential nutrient, was found to effectively reduce the severity of some fetal alcohol effects, even when administered after the ethanol insult was complete. NIH also is investing in a large-scale prospective study looking at prenatal alcohol exposure along with other maternal risk factors in adverse pregnancy outcomes. Following a 3-year feasibility study, NIH established the Prenatal Alcohol, Sudden Infant Death Syndrome, and Stillbirth (PASS) Research Network, a multidisciplinary consortium to determine the role of prenatal alcohol exposure and other maternal risk factors in the incidence and etiology of sudden infant death syndrome (SIDS), stillbirth, and fetal alcohol syndrome, all of which are devastating pregnancy outcomes. The PASS study prospectively will follow 12,000 pregnant, high-risk, American Indian and South African women and their infants until the infants are 12 months old. Maternal, fetal, and infant measures and tissues will be obtained for analysis.

- For more information, see <http://www.nichd.nih.gov/research/supported/pass.cfm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Minority Health and Health Disparities*
- (E) (NIAAA, NICHD)

Strategies to Manage and Prevent Food Allergies: Food allergy occurs in approximately 4.7 percent of children under 5 years of age and in 3.7 percent of children 5 to 17 years of age. Allergies to peanuts and tree nuts, the allergens most relevant to severe food allergy and anaphylaxis, occur in approximately 1 percent of children and adults. Severe whole-body allergic reactions, also known as anaphylaxis, are a frequent cause of emergency room visits, many of which are attributed to food allergy. Every year in the United States, it is estimated that there are approximately 15,000-30,000 episodes of food-induced anaphylaxis. NIH seeks to understand better both the immune system response to food allergies and how certain foods trigger an allergic reaction. Researchers in the United States and abroad are conducting clinical trials to improve management of allergy to cow's milk, egg, and peanut, and innovative clinical trials are assessing strategies to prevent development of peanut allergies. One important trial will determine whether early and regular consumption of a peanut snack by infants and very young children at risk of developing peanut allergy will promote tolerance and prevent the development of this allergy. In FY 2008, NIH sought to bring new investigators into the field through the Exploratory Investigations in Food Allergy initiative, which supports innovative pilot studies and developmental research on the mechanisms of food allergy. The program will be recompeted in FY 2010. During this period, NIH continued funding for the Consortium of Food Allergy Research, which supports basic, preclinical, and clinical research to assess the pathophysiology and natural history of food allergy-associated anaphylaxis and to develop interventions to prevent and treat food allergy.

- For more information, see <http://www3.niaid.nih.gov/topics/foodAllergy/default.htm>

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NIAID)

Eye Disease Burden Data from National Health and Nutrition Examination Survey (NHANES): The CDC uses rigorous national surveys such as NHANES to collect information on the health of the U.S. population. In 1999, NIH and CDC collaborated to add estimates of vision impairment to NHANES. Based on an analysis of baseline NHANES data from 1999-2004, it was estimated that half of the U.S. population over the age 20 years has blurry vision, called refractive errors (nearsightedness, farsightedness, and/or astigmatism). Refractive errors can be corrected with eyeglasses, contact lenses, or surgery to restore clear vision. After 2004, a new survey was developed to capture information on more severe visual impairments, the extent of uncorrected (but correctable) refractive errors, the methods individuals selected to correct refractive error, and vision-related quality-of-life questions. These changes will improve estimates of the extent and nature of vision impairment in the United States. The effort to develop visual impairment statistics is consistent with an NIH GPRA goal to "develop stable national estimates of vision impairment by extending the vision component of NHANES."

- Vitale S, et al. *Arch Ophthalmol* 2008;126(8):1111-9. PMID: 18695106. PMCID: PMC2772054.
- For more information, see <http://archophth.ama-assn.org/cgi/content/full/126/8/1111>
- For more information, see <http://www.cdc.gov/nchs/nhanes.htm>
- (I, O) (NEI) (GPRA)

End-Stage Renal Disease: According to the United States Renal Data System—an NIH-supported national data system that collects, analyzes, and distributes information about people with kidney failure—more than one-half million Americans suffer from kidney failure. Patients with this condition—known as end-stage renal disease or ESRD—require a kidney transplant or hemodialysis, a process that uses a machine to remove waste products and excess fluid from the bloodstream. To facilitate hemodialysis, some patients undergo a surgical procedure to create a site on the body that allows easy, repeated access to the blood vessels. However, over time, many vascular access sites become unusable and fail. The NIH-supported Dialysis Access Consortium found that treatment with an anti-blood clotting drug did not improve the long-term suitability of a type of access known as a fistula. A separate study by the consortium found that the long-term usability of a different type of access site, known as a graft, could be improved through treatment with a combination of aspirin and another anti-clotting drug. Still, important questions remain. To better understand the underlying biology of access site maturation, NIH is launching a Vascular Biology of Hemodialysis Vascular Access Consortium to study the molecular and cellular pathways that contribute to vascular injury and high rates of vascular access failure. Such research may inform new strategies to improve outcomes in patients undergoing hemodialysis.

- Dember LM, et al. *JAMA* 2008;299(18):2164-71. PMID: 18477783.
- Dixon BS, et al. *New Engl J Med* 2009;360(21):2191-201. PMID: 19458364.
- For more information, see <http://www.usrds.org>
- For more information, see <http://www.nih.gov/news/health/may2008/niddk-22a.htm>
- For more information, see <http://www.nih.gov/news/health/may2009/niddk-20.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDDK)

Research on Bariatric Surgery: The multicenter NIH-funded Longitudinal Assessment of Bariatric Surgery (LABS) consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Results from this study have been published in the *New England Journal of Medicine*. The study also addresses comparative effectiveness with respect to its collection of data on surgical procedures and pre- and post-operative information. Because bariatric surgery also is used in clinical practice sometimes as a treatment for severely obese adolescents,

Epidemiological and Longitudinal Studies

NIH additionally is supporting an observational study of teens already scheduled for surgery, Teen-LABS, to collect data to help determine whether it is an appropriate treatment option for extremely obese adolescents. A pilot study also is being conducted using the new Metabolic Clinical Research Unit at the NIH CC to examine changes in insulin resistance after bariatric surgery. To further explore the observation that certain bariatric surgical procedures are associated with amelioration of obesity-related insulin resistance and diabetes soon after surgery, and thus independent of weight loss, NIH issued a funding opportunity announcement to encourage research in this area.

- Adams TD, et al. *N Engl J Med* 2007;357(8):753-61. PMID: 17715409.
The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. *N Engl J Med* 2009;316(5):445-54. PMID: 19641201.
- For more information, see <http://win.niddk.nih.gov/publications/labs.htm>
- For more information, see <http://www.nih.gov/news/pr/apr2007/niddk-16.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NIDDK, ORWH)

The Hispanic Community Health Study: In October 2006, NIH began the largest long-term epidemiological study of health and disease ever conducted in people of Hispanic/Latino heritage living in the United States. The study includes 16,000 participants of diverse Hispanic/Latino background, including Mexican, Cuban, Puerto Rican, and Central/South American. It is designed to identify factors that render these groups either susceptible to or protected from heart disease, stroke, asthma, chronic obstructive pulmonary disease, sleep disorders, dental disease, hearing loss, diabetes, kidney and liver disease, cognitive impairment, and other chronic conditions. Recruitment started in March 2008 in four cities. Variables such as height, weight, and other body measurements; blood pressure; blood lipids and glucose levels; diet; physical activity; smoking; acculturation; socioeconomic status; psychosocial factors; occupational history and exposure; access to and use of health care services; and use of medications and dietary supplements currently are being assessed.

- For more information, see <http://www.csc.unc.edu/hchs>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
- (E) (NHLBI, NCMHD, NIDCD, NIDCR, NIDDK, NINDS, ODP/ODS)

The Multi-Ethnic Study of Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter epidemiological study of cardiovascular disease (CVD) in 6,914 men and women from 4 ethnic groups—white, African-American, Hispanic, and Chinese—who have been followed for almost 10 years to identify predictors of progression of subclinical CVD. The study originally was funded from 1999 to 2008 and subsequently renewed through 2015. It has measured and compared the predictive value of chest computed tomography, cardiac magnetic resonance imaging, carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for the development of CVD. MESA has major ongoing ancillary studies in the areas of air pollution (funded by the EPA), chronic lung disease, and genetics. MESA SHARe (SNP Health Association Resource) will combine genome-wide scans with detailed phenotypic information and share these data with the scientific community for genome-wide association analyses.

- For more information, see <http://mesa-nhlbi.org>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Genomics*
- (E) (NHLBI, NEI)

Culture of Cooperation to Promote Public Health

Research Initiatives to Study Suicidality and Mental Health Needs of U.S. Army Soldiers and Returning Combat Veterans:

The high rates of mental health and behavioral adjustment problems among recent U.S. military combat veterans, and the increasing rates of suicide among Army soldiers, are of growing concern. To address these issues, NIH is collaborating with the U.S. Army to evaluate selected groups of soldiers across all phases of Army service, including entry-level training and service, pre-deployment training, deployment and noncombat assignments, post-deployment, and post-separation reintegration to civilian life. The study's intent is to identify modifiable risk and protective factors, as well as moderators, of suicide-related behaviors. NIH also is launching a study of the impact of existing national, state, and local community-based programs addressing the adjustment and mental health needs of recent combat veterans, including returning National Guard, Army Reserve, and newly separated active duty personnel. This initiative will produce new information concerning effective strategies for fostering successful transition from combat to civilian roles for returning service members.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-140.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-070.html>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIMH)

Diabetes and Pesticide Exposure/the Agricultural Health Study: Exposure to certain pesticides increased the risk of diabetes in licensed applicators, according to researchers from NIH. The investigation of applicators enrolled in the Agricultural Health Study is the largest study to date to evaluate potential effects of pesticides on diabetes incidence in adults. Because previous studies using data from the National Health and Nutrition Examination Survey (NHANES) found associations of diabetes with serum levels of persistent organic pollutants, the researchers wanted to know if there was a similar association between diabetes and lifetime exposure to pesticides. Therefore, they evaluated applicators who reported diabetes for the first time in 5-year follow-up telephone interviews, conducted between 1999 and 2003. Previously, applicators had described use of 50 different pesticides, providing information on 2 primary measures: ever use and cumulative lifetime days of use. Of 50 pesticides evaluated, 7 were associated with an increased incidence of diabetes using both exposure measures. Three of these were organochlorine insecticides (aldrin, chlordane, heptachlor), 2 were organophosphate insecticides (trichlorfon, dichlorvos), and 2 were herbicides (alachlor, cyanazine). The strongest association was with trichlorfon: Applicators who had used the chemical on more than 10 days in their lifetime had a 2.5-fold increase in risk. Pesticide applicators who reported exposure to these pesticides showed an increased risk of diabetes independent of age, state of residence, and body mass index. The increasing burden of diabetes in populations worldwide warrants an improved understanding of the possible relation of diabetes risk to long-term, low levels of pesticide exposure.

- Montgomery MP, et al. *Amer J Epidemiol* 2008;167:1235-46. PMID: 18343878.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E/I) (NIEHS, NCI)

EARLI, the Early Autism Risk Longitudinal Investigation: EARLI, the Early Autism Risk Longitudinal Investigation, comprises a network of leading autism researchers from three regions across the country. EARLI is following a cohort of 1,200 mothers of children diagnosed with autism who are pregnant or planning a pregnancy. The EARLI network will study how genetics and environmental factors work together to cause autism by studying families who already are affected by autism. Data will be collected prospectively via clinical assessment, interviews, self-reports, medical record review, home environment assessments, and biologic samples that will be used in current analysis and stored for future studies. Planned analyses include a determination of whether in utero exposure to organic pollutants such as polychlorinated biphenyls (PCBs), brominated diphenyl ethers (BDEs), and persistent organic pollutants (POPs) is associated with autism risk.

Epidemiological and Longitudinal Studies

- For more information, see <http://earlistudy.org>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIEHS)

Addressing Drug Abuse and Comorbidities in Returning Vets and Their Families: Sustained U.S. combat operations in Afghanistan and Iraq have resulted in military personnel experiencing increased numbers and lengths of deployments and greater exposure to traumatic stressors. Stress can be a major contributor to both the onset and exacerbation of substance abuse and other mental health problems, and can lead to relapse in former substance abusers. To understand better the intervention needs of this group, NIH in 2009 sponsored a 2-day meeting to formulate a research agenda for conducting addiction prevention and treatment research with military and veteran populations and their families. Collaborators included the U.S. Army Medical Research and Materiel Command, the Department of Defense Health Affairs, the Army Center for Substance Abuse Programs, the Department of Veterans Affairs, and several NIH ICs. Subsequently, a call for studies on trauma, stress, and substance use and abuse among U.S. military personnel, veterans, and their families was issued. It focuses on epidemiology/etiology, screening and identification, and prevention and treatment of substance use and abuse—including alcohol, tobacco, and other drugs—and associated problems (e.g., PTSD, traumatic brain injury, sleep disturbances, and relationship violence) among U.S. military personnel, veterans, and their families. Further, NIH's National Drug Abuse Treatment Clinical Trials Network (CTN) is developing a protocol concept for the treatment of PTSD and drug abuse/dependence in veteran populations. It is expected that this study will be conducted in clinics participating in the CTN, which include some Veterans Administration hospitals and research facilities.

- For more information, see <http://www.drugabuse.gov/pdf/tib/veterans.pdf>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDA, NCI, NIAAA, NIMH)

Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer Care: The purpose of the Cancer Research Network (CRN) is to enhance research on cancer epidemiology, prevention, early detection, and control in the context of health care delivery systems. CRN combines established research groups affiliated with 14 health care delivery organizations that provide comprehensive care to a racially and ethnically diverse population of nearly 11 million individuals. CRN has developed strong research capabilities in several areas: developing and applying innovative methods to collect and interpret data from both conventional and electronic medical records systems; assembling large samples of patients with documentation of patient characteristics and longitudinal data on receipt of health services and clinical and quality-of-life outcomes; collecting and integrating complex data from patients, providers, and organizations to examine issues in health care delivery from multiple perspectives; quantifying the effect of key factors in the delivery process that may determine quality and outcomes of care; and conducting studies on behavioral and systems-based interventions to improve the delivery of care in community-based health care delivery systems. The Breast Cancer Surveillance Consortium (BCSC) is a research resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. The BCSC is a collaborative network of seven mammography registries with linkages to tumor and/or pathology registries. The Consortium's database contains information on 7,521,000 mammographic examinations, 2,017,869 women, and 86,700 cancer cases.

- For more information, see <http://crn.cancer.gov>
- For more information, see <http://breastscreening.cancer.gov/>
- This example also appears in Chapter 2: *Cancer*, Chapter 3: *Clinical and Translational Research* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (NCI)

Population Genomics, GAIN, and GEI: In 2006, HHS announced the creation of two groundbreaking initiatives for population genomics research in which NIH played a leading role. The Genetic Association Information Network (GAIN) was a public-private partnership involving NIH, the Foundation for NIH, Pfizer, Affymetrix, Perlegen, the Broad Institute, and Abbott. GAIN supported a series of genome-wide association studies designed to identify specific points of DNA variation associated with the occurrence of common diseases. Investigators from existing clinical studies were invited to submit samples and data on roughly 2,000 participants for genomic assays designed to capture roughly 80 percent of the common changes in the human genome. GAIN successfully concluded in November 2008, with the third and final public workshop on the project. At this meeting, investigators from across the research community shared their findings and discussed how they had used the data generated through GAIN in their own research. Data from the GAIN studies have been deposited into the NIH database of Genotype and Phenotype (dbGaP) for the broad use of the research community. Access is controlled by the GAIN Data Access Committee. Additionally, NIH funds the Genes, Environment, and Health Initiative (GEI), an NIH-wide effort combining comprehensive genetic analysis and environmental technology development to understand the causes of common diseases. GEI has held a number of workshops to identify novel ways of analyzing the wealth of information gathered and to use that data to improve human health.

- For more information, see <http://www.genome.gov/19518664>
- For more information, see <http://www.genome.gov/19518663>
- For more information, see <http://genesandenvironment.nih.gov>
- For more information, see <http://www.genome.gov/11511175>
- This example also appears in Chapter 3: *Genomics*
- (E, I) (NHGRI, NIEHS, NLM)

Urology Research: The Urinary Incontinence Treatment Network (UITN) conducts long-term studies and clinical trials of the most commonly used surgical, pharmacological, and behavioral approaches for management of urinary incontinence in women diagnosed with stress and mixed incontinence. Recently, a different group of investigators completed the Program to Reduce Incontinence by Diet and Exercise (PRIDE) study and determined that a weight loss program could reduce significantly the frequency of urinary incontinence in overweight and obese women. Several studies address interstitial cystitis/painful bladder syndrome (IC/PBS), a urologic condition whose prevalence is uncertain and which remains difficult to diagnose and treat. The RAND Interstitial Cystitis Epidemiology (RICE) study is designed to estimate the prevalence of interstitial cystitis and establish a working definition of this condition. The Boston Area Community Health (BACH) Survey is a population-based study of urologic conditions, including IC/PBS, in more than 5,500 adults. Results emerging from BACH about IC/PBS will provide a clearer picture on the IC/PBS burden in the population, and will inform research efforts to reverse this burden. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is designed to enhance understanding of the major urological chronic pelvic pain disorders, including IC/PBS and chronic prostatitis/chronic pelvic pain syndrome.

- Burgio KL, et al. *Ann Int Med* 2008;149:161-9. PMID: 18678843.
- Subak LL, et al. *N Eng J Med* 2009;360(5):481-90. PMID: 19179316.
- For more information, see <http://www.uitn.net/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (NIDDK, NICHD)

According to a Government Survey, 38 Percent of Adults and 12 Percent of Children Use Complementary and Alternative Medicine: In December 2008, NIH and the National Center for Health Statistics released new findings on Americans' use of complementary and alternative medicine (CAM). The findings are from the 2007 National Health Interview Survey (NHIS), an annual in-person survey of Americans regarding their health- and illness-related experiences. According to the survey, approximately 38 percent of adults and nearly 12 percent of children use some form of CAM. For

Epidemiological and Longitudinal Studies

both adults and children, the most commonly used type of CAM is nonvitamin/nonmineral natural products, and the most common use for CAM is to treat pain. Although overall use of CAM among adults has remained relatively stable since 2002 (the last time NHIS included a CAM section), the use of some specific CAM therapies has varied substantially; for example, deep breathing, meditation, massage therapy, and yoga have all shown significant increases. The 2007 NHIS was the first to ask about CAM use by children. The NHIS also reports on characteristics of CAM users, such as gender, age, education, geographic region, poverty status, and health indicators. The 2007 NHIS provides the most current, comprehensive, and reliable source of information on Americans' use of CAM. These statistics confirm that CAM practices are a frequently used component of American's health care regimens, and reinforce the need for rigorous research to study the safety and effectiveness of these therapies. The data also point out the need for patients and health care providers to openly discuss CAM use to ensure safe and coordinated care. Future analyses of these data may help explain some of the observed variation in the use of individual CAM therapies and provide greater insights into CAM use patterns among Americans.

- Barnes PM, et al. *Natl Health Stat Report* 2008;(12):1-23. PMID: 19361005.
- For more information, see <http://www.cdc.gov/nchs/data/nhsr/nhsr012.pdf>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NCCAM, CDC)

Half of Surveyed Physicians Use Placebo Treatments for Patients: Treating patients with placebos has a long, complicated, and often controversial history. Nonetheless, little actually is known about U.S. physicians' current attitudes toward and use of placebo treatments. A national survey funded in part by NIH looked at placebo-prescribing practices among 679 internists and rheumatologists—specialties that commonly treat patients with debilitating chronic conditions. The survey found that about half of the physician respondents prescribed placebo treatments on a regular basis. Most (62%) said they think the practice is ethical. Among physicians who prescribed placebos, few said they used inert treatments such as saline injections or sugar pills; they were more likely to recommend over-the-counter analgesics (41%) or vitamins (38%), and some used antibiotics (13%) or sedatives (13%) as placebos. The survey also found that the physicians who used placebos rarely described them as such to patients. Instead, physicians most commonly described the treatments as medicine that typically is not used for the patient's condition but that might be beneficial. The survey provides insights into the complex relationship between placebo use and physicians' traditional role in promoting positive expectations in their patients. It also raises concerns about the use of "active" placebos, particularly antibiotics and sedatives, when they are not medically indicated. Prescribing placebo treatments remains an appropriate topic for ethical and policy debates.

- Tilburt JC, et al. *BMJ* 2008 Oct 23;337:a1938. PMID: 18948346. PMCID: PMC2572204.
- For more information, see <http://nccam.nih.gov/research/results/spotlight/102408.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NCCAM)

Study Shows One-Fifth of Internet-Available Ayurvedic Medicines Contain Toxic Metals: Ayurveda, a traditional medical system that originated in India, aims to integrate and balance the body, mind, and spirit to help prevent illness and promote wellness. Potentially toxic metals sometimes are incorporated in traditional Ayurvedic medicines as part of *rasa shastra*—a practice that combines herbs with metals, minerals, and gems. In an NIH-funded study, researchers sought to determine how often Ayurvedic medicines sold on the Internet contain detectable levels of lead, mercury, and arsenic. They purchased products manufactured in both India and the United States and examined both *rasa shastra* and *nonrasa shastra* (herbal-only) medicines. Using 5 different search engines, the researchers found 25 websites that sold traditional Ayurvedic herbs, formulas, and ingredients. Of the 230 products randomly selected for purchase, 193 were received and

tested for the presence of metals. Nearly 21 percent of the Ayurvedic medicines tested were found to contain detectable levels of lead, mercury, or arsenic. Rasa shastra products were more than twice as likely as nonrasa shastra products to contain metals, and several rasa shastra medicines manufactured in India could result in lead and/or mercury ingestion 100 to 10,000 times greater than acceptable limits. This study's findings lend support to the value and importance of rigorous standards of product quality and self-regulation within the herbal medicine and dietary supplement industry. The authors call for strictly enforced, government-mandated, daily-dose limits for toxic metals in all dietary supplements, and requirements that all manufacturers demonstrate compliance through third-party testing.

- Saper RB, et al. *JAMA* 2008;300(8):915-23. PMID: 18728265. PMCID: PMC2755247.
- For more information, see <http://nccam.nih.gov/research/results/spotlight/082808.htm>
- (E) (NCCAM)

SNP-Health Association Resource (SHARe): SHARe conducts genome-wide association studies in several large NIH cohort studies to identify genes underlying cardiovascular and lung diseases and other disorders such as obesity and diabetes. The resulting genotype data along with the cohort phenotype data are made available to researchers around the world through the NIH dbGAP database. Framingham SHARe, with 9,000 participants, was the first cohort released in this initiative due to its uniqueness in including 3 generations of participants with comparable data obtained from each generation at the same age. As of October 31, 2009, 95 projects to use these data had been approved. A modified version of the dataset was distributed to 72 approved research projects as the focus of a Southwest Foundation Genetic Analysis Workshop. The second cohort released was the SHARe Asthma Resource Project, which includes genotype data from more than 2,500 adults and children who have participated in NIH clinical research trials on asthma. As of October 31, 2009, 11 projects to use these data had been approved. Data from more than 12,000 African-American and Hispanic women from the Women's Health Initiative and approximately 8,300 participants from the Multi-Ethnic Study of Atherosclerosis were released in January 2010.

- For more information, see <http://www.nih.gov/news/pr/oct2007/nhlbi-01.htm>
- For more information, see <http://nih.gov/news/health/dec2008/nhlbi-15.htm>
- For more information, see <http://view.ncbi.nlm.nih.gov/dbgap/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
- (E) (NHLBI, NLM)

Epidemiological and Longitudinal Studies

- ¹ Hayes RB, et al. *J Natl Cancer Inst* 1997;89(14):1065-71. PMID: 9230889.
- ² Lan Q, et al. *Science* 2004;306(5702):1774-6. PMID: 15576619. PMCID: PMC1256034.
- ³ U.S. Environmental Protection Agency. Control of hazardous air pollutants from mobile sources: final rule to reduce mobile source air toxics. EPA420-F-07-01. February 2007. Available at <http://www.epa.gov/oms/regs/toxics/420f07017.htm#program>. Accessed July 30, 2009.
- ⁴ The NS, Gordon-Larsen P. *Obesity* 2009;17(7):1441-7. PMID: 19360012. PMCID: PMC2745942.
- ⁵ Thomas G, et al. *Nat Genet* 2009;41(5):579-84. PMID: 19330030.
- ⁶ Thomas G, et al. *Nat Genet* 2008;40(3):310-5. PMID: 18264096.
- ⁷ Yeager M, et al. *Hum Genet* 2008;124(2):161-70. PMID: 18704501. PMCID: PMC2525844.
- ⁸ National Institute on Drug Abuse. Monitoring the Future National Results on Adolescent Drug use: Overview of Key Findings 2008. Available at: <http://www.monitoringthefuture.org/index.html>. Accessed July 29, 2009.
- ⁹ National Institute on Aging. Growing Older in America: The Health & Retirement Study. March 2007. Available at <http://hrsonline.isr.umich.edu/index.php?p=dbook>. Accessed July 29, 2009.
- ¹⁰ Caffrey C, Himes CL. *J Aging Soc Policy* 2008;20(1):29-44. PMID: 18198158.
- ¹¹ Detrano R, et al. *N Engl J Med* 2008;358(13):1336-45. PMID: 18367736.
- ¹² Hoppin JA, et al. *Eur Respir J* 2009;34(6):1296-303. PMID: 19541724. PMCID: PMC2822385.
- ¹³ Montgomery MP, et al. *Am J Epidemiol* 2008;167(10):1235-46. PMID: 18343878. PMCID: PMC2832308.

Genomics

When the United States launched a massive effort to sequence the human genome in 1990, many said it could not—or should not—be done. Skeptics feared that the cost would be too high, draining funds from other, more promising research. They warned that adequate technology did not exist to complete the project, and that the cost of developing the necessary technology was unworkable. Methods of sequencing DNA were barely past the laboratory-bench stage and cost about \$10 for each base pair (bp); at that rate, sequencing a human genome would cost at least \$30 billion. Moreover, the prevailing wisdom was that most of the genome was meaningless "junk" that could be ignored, rather than "coding areas"—the genes—that instruct cells in the body how to make proteins.

But one of the earliest goals of the Human Genome Project was to boost the speed and cut the cost of sequencing DNA. By 2004, newly developed technology could sequence a full genome for just \$20 million. By 2009, even newer sequencing machinery could do the job for \$100,000. Now, NIH is on track to achieve its goal of technology that can sequence an individual patient's DNA for \$1,000—less than the price tag of some high-tech medical tests today—which will usher in a new era of medicine. (And along the way, scientists are learning that the "junk" is very important indeed.)

Introduction

Genomics is the study of an organism's entire genome—the complete assembly of DNA (deoxyribonucleic acid), or in some cases RNA (ribonucleic acid)—that transmits the instructions for developing and operating a living organism. Genomic research focuses not just on individual genes but also on the functioning of the entire genome as a network and, importantly, on how this network interacts with environmental factors to influence health and cause disease. Genomics is a new and challenging discipline that is increasingly used in virtually every field of biological and medical research.

DNA is made up of four chemical compounds called "nucleotides"—adenine, thymine, guanine, and cytosine—denoted by the letters A, T, G, and C respectively. These nucleotides are assembled in two parallel strands in the form of a double helix. Each nucleotide in one strand always links to the same partner on the other strand: A always pairs with T; C always pairs with G. Each of these pairings is referred to as a "base pair." The human genome consists of about 3 billion base pairs, packaged in 23 sets of chromosomes, wrapped extremely tightly into the nucleus of virtually every cell in the body. Identifying the base pairs—and thus the letters—and the order in which they appear on any stretch of DNA is called "sequencing" that segment.

DNA's double helical structure was discovered in 1953. The human genome was fully sequenced 50 years later, in 2003, by a 13-year, U.S.-led multinational effort called the Human Genome Project, which ended ahead of schedule and under budget. The sequencing of the human genome generated immense scientific excitement. It provided a new means of analyzing the functions of cells, tissues, and systems in the body and offered new tools for understanding the causes of disease. It laid the foundation for broad new scientific disciplines such as proteomics, the study of the structure and function of all the proteins produced by the body (in response to instructions carried by the genes). Recent studies have demonstrated that the genome contains more information than can be interpreted from just its sequence. It is more complex, more variable in its structure, and more complicated in its internal interactions than anyone imagined just a few years ago.

Almost every human disease or disorder has a genetic component and an environmental component. The genetic component for some heritable diseases, such as sickle cell disease or cystic fibrosis, result from mutations in single genes—changes that disrupt the function of the protein they encode. However, in most diseases the role of genes and the environment is more complicated. Some diseases arise as a result of spontaneous gene mutations that occur during a person's lifetime; others are caused by complex cascades of changes in gene expression triggered, perhaps, by environmental factors. Differences as small as one letter in our 3 billion pairs of DNA letters can cause disease directly or

make people respond differently to particular pathogens or drugs. Multiple genetic and environmental factors play a role in myriad common diseases, such as heart disease, cancer, and asthma, but for no common disease have all the genes involved yet been identified.

Educational resources, including multimedia presentation, to help the public understand genomics are available on the NIH website.

As a result of the overwhelming influence of the genome on human health, virtually every NIH Institute and Center now engages in genome-related research.

As a result of the overwhelming influence of the genome on human health, virtually every NIH IC now engages in genome-related research. Like many NIH Institutes, NCI supports a huge array of gene-oriented projects, including Genome-Wide Association Studies (GWAS)—in effect, full-body DNA scans—that recently detected new genetic factors involved in breast, prostate, and colon cancers. Over the past 2 years, NHLBI and NIGMS have sponsored a research consortium that combined both genetic and clinical data to devise a computer algorithm for setting the proper dose of the blood-thinner warfarin, commonly prescribed for heart patients and others.¹⁴ A major clinical trial began in early 2009 to test whether that new algorithm is better than the current trial-and-error method. NIMH-supported researchers recently identified a stretch of DNA (on chromosome 6) that appears to be implicated in both schizophrenia and bipolar disorder—a finding that may aid the search for treatments and suggests that both disorders flow from errors in wiring the brain during fetal development, potentially opening a new line of research.^{15, 16, 17} NIAID now has sequenced the genomes of thousands of infectious microorganisms, including 4,000 influenza viruses; within a few months of the emergence of the 2009 H1N1 influenza—the so-called "swine flu" virus—in early 2009, it had sequenced nearly 1,000 separate H1N1 strains.

Within a few months of the emergence of the 2009-H1N1 influenza—the so-called "swine flu" virus—in early 2009, NIH had sequenced nearly 1,000 separate H1N1 strains.

NIH researchers and grant recipients also have increased the pace of sequencing other nonhuman genomes. Full sequences of nearly 200 organisms now have been completed or are underway, and not just the genomes of our close primate relatives such as the chimpanzee. Between 2007 and 2009, NIH-supported scientists completed sequencing the genomes of 16 invertebrates, 1 mammal, and the egg-laying duck-billed platypus—whose genome retains many reptilian features—and selected 34 new organisms for full-genome sequencing. Comparing the human genome to the genomes of other creatures, including insects and even single-celled organisms, reveals stretches of DNA that have remained similar over millions of years of evolution. These "conserved" sequences are thought to play an important role in the functioning of a living organism, even if scientists do not yet know what that role is.

Genes themselves, the "coding regions" of DNA that direct cells to make particular proteins, account for only about 2 percent of the human genome. Locating the noncoding but functional sequences throughout the rest of the genome is the main mission of the ENCODE research consortium (the acronym stands for **ENC**yclopedia **Of DNA Elements**). NIH also has pressed ahead with the Model ENCODE project (modENCODE) to identify all the functional elements in the genomes of two hugely important and widely used laboratory model organisms—the fruit fly *Drosophila melanogaster* and the roundworm *Caenorhabditis elegans*.¹⁸ The strategy is that identifying genomic mechanisms in these model organisms will elucidate novel research directions for human genomic and other researchers. (Also see the section on *Molecular Biology and Basic Research* in Chapter 3.)

Approaching the Era of Personalized Medicine

DNA sequencing and analysis projects serve another purpose as well: advancement of technology and bioinformatics that may soon bring revolutionary improvements to the practice of medicine. The development of new methods to sequence DNA faster and more cheaply is the central goal of some NIH-sponsored projects, and as NIH has continued to fund technological innovation in this area, the costs have continued to fall remarkably. Soon, when a patient's full genome can be sequenced for less than the cost of other routine medical tests, and when ongoing genomic research programs have further broadened and deepened our understanding of the genome's functioning, medical science will stand on a new plateau. The practice of medicine will move beyond a one-size-fits-all approach—and the promise of personalized medicine will be realized. One application of personalized medicine is pharmacogenomics, which seeks to understand the inherited variations in genes that dictate drug response. Furthermore, it explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a poor or adverse response to a drug, or no response at all. By understanding the differences in the genetic basis of drug responses, scientists hope to enable doctors to prescribe the drugs and doses best suited for each individual. The mission of the NIH Pharmacogenetics Research Network (PGRN) is to better understand the genetic basis for variable drug responses and identify safe and effective drug therapies designed for individual patients.

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Most of the genome research that will yield direct clinical implications, improve our understanding of human health, and change clinical practice still lies ahead. However, over the next decade, research will unlock the true potential of this foundational work, leading scientists closer to better means for preventing, diagnosing, and treating disease.

Summary of NIH Activities

Among NIH's key activities and accomplishments in the field of genomics in FYs 2008-2009 were those involving the following:

- **New Genome-Wide Association Studies (GWAS).** Using DNA from tissue samples, GWAS scan and compare entire genomes of people with and without a particular disease, looking for single-base differences (known as single nucleotide polymorphisms, or SNPs) that might signal the presence of a gene or some other functional sequence implicated in the disease. GWAS are based on the Haplotype Map (HapMap) of the human genome, produced via an NIH-led international research team earlier in the decade that identified more than 3 million relatively common SNPs in human genomes that serve as markers for larger neighborhoods of DNA sequences. GWAS scans point to regions of the genome that are worthy of closer study in seeking the genetic cause of a disease. Hundreds of such studies have been conducted since the technique was first developed in 2005, flagging genetic areas that may be linked with at least 80 different diseases and disorders including heart disease, diabetes, obesity, and many types of cancer. In 2008 alone, GWAS identified more than 130 genetic factors involved in human disease. Among the GWAS currently under way is an effort to determine the genes involved in HIV disease progression and susceptibility to HIV acquisition.
- **The 1,000 Genomes Project.** This international research consortium assembled and led by NIH began sequencing the genomes of at least 1,000 people to improve dramatically on the current HapMap. The HapMap pinpoints DNA variations that are present in 5 percent or more of humans. The 3-year, 1,000 Genomes Project will achieve a finer resolution, creating a catalog of variations that are present in as few as 1 percent of people. It will focus even more tightly on the coding regions of genes, locating variations that are present in as few as 0.5 percent of individuals. Importantly, the new project will catalog not just SNPs but also structural variations in human DNA, such as deletions, duplications, and rearrangements of DNA sequences.
- **Structural variation.** Scientists have gathered increasing evidence that the genome is not a string of independently operating genes, but rather is a hugely complicated, integrated whole, and that variations in the structure of the chromosomes have a major impact on human health. Yet, the mechanisms involved are not fully understood. In 2008, an NIH-supported research consortium produced the first sequence-based map of large-scale structural variations,

ranging from a few thousand bases to several million.¹⁹ These include deletions of whole genes, repetitions of sequences (sometimes multiple repetitions), and rearrangements of stretches of DNA. Some variants already have been linked to diseases, such as coronary heart disease, schizophrenia, and autism, and to differences in susceptibility to HIV infection.

- **New disease genes.** NIH researchers have identified individual genes or regions of DNA associated with, among other diseases and disorders: schizophrenia and bipolar disorder; cancers of the skin, lung, brain, pancreas, breast, prostate, and testicle, and acute lymphoblastic leukemia; diabetes; periodontitis in African Americans; asthma; high blood pressure; heart arrhythmias; Crohn's disease; obesity; and many others.
- **Clinical genomics.** NIH began a large pilot project to test ways that high-throughput genome sequencing might be used in a clinical setting for diagnosing and treating patients. Using the NIH Clinical Center, the trial, dubbed "ClinSeq" (for **clinical sequencing**) will enroll an initial 1,000 patients with a spectrum of coronary artery calcification from normal to diseased and will sequence 200 to 400 areas of their DNA that contain genes suspected of involvement in heart disease. Patients will have the option of learning the outcome of their tests, and those who carry a variant of a gene that has been linked to disease will be counseled and followed up, possibly for years. The study is designed both as a pilot project to explore ways of using genome sequencing in patient treatment and as an effort to develop new data about particular genes' involvement in heart disease. The project may expand in its later stages to cover other diseases.
- **Consumer interest.** ClinSeq is not the only way that NIH is exploring whether people want to know what genomics might have to tell them. In a program known as the Multiplex Initiative, individuals ages 25 to 40 are offered free testing for 15 genes associated with higher risk for type 2 diabetes, heart disease, high cholesterol, high blood pressure, osteoporosis, lung cancer, colorectal cancer, and malignant melanoma. Those who are offered the testing use an interactive, Internet-based program designed by NIH researchers that helps participants ask questions about the genetic testing, get information, and decide whether to receive the testing. Meanwhile, Multiplex Initiative researchers monitor the participants' decision process every step of the way. Those who decide to submit blood samples for the tests will be followed for some time afterward to see whether they change their behavior (for example, by adopting a healthier lifestyle or diet) in response to their test results.²⁰ Researchers involved with this study have found that individuals who discuss their genetic information with their doctors may be among the most motivated to take steps toward more healthy choices.
- **Pharmacogenetics.** NIH launched a major clinical trial to test a gene-based method of prescribing warfarin, a blood thinner that is widely used to prevent life-threatening blood clots. About 2 million Americans start taking warfarin each year, but the drug's effect on individual patients is notoriously variable. Regular blood tests are needed both to establish an initial dose level and to maintain the proper level as time goes on—for months and often for years. In early 2009, an international research consortium combined patients' genetic and clinical data to produce a computer algorithm that appeared to be more accurate than basing the initial dose on a patient's clinical condition alone and then increasing or decreasing the dose to achieve the optimal blood level.¹ NIH quickly began a multicenter clinical trial, known as the Clarification of Optimal Anticoagulation through Genetics (COAG) trial, to compare the gene-based method with the current trial and error approach in a much wider pool of patients. COAG will enroll 1,200 patients of varying backgrounds at 12 sites and will follow them for 6 months. Its outcome could improve protection against heart attacks and strokes for millions of Americans.
- **Nonhuman genomes.** NIH completed full sequencing and analysis of multiple vertebrate and invertebrate animal genomes in 2008-2009. These include the platypus, domestic cattle, the wasp, other insects, and a large number of disease-causing organisms—such as the malaria-causing parasite *Plasmodium vivax*, the common intestinal parasite *Giardia lamblia*, the Lyme disease-causing tick *Ixodes scapularis*, and two species of the parasitic flatworms that cause schistosomiasis. Also sequenced were thousands of separate strains of the constantly changing human influenza viruses. Molecular comparisons of the 2009 H1N1 influenza and other flu strains may help scientists learn how 2009 H1N1 is evolving, how it is interacting with other strains, and whether it is gaining or declining in virulence.
- **Health Disparities.** NIH-funded analysis of genomic data from 121 African populations, 4 African American populations, and 60 non-African populations revealed that all African populations descended from 14 ancestral groups. Most African Americans trace the majority of their ancestry to West Africa, a finding that will improve scientists' ability to identify genetic risk factors in African and African American populations.

Identifying Microbial Free-Riders: The Human Microbiome Project

Among the newer NIH initiatives is the 5-year Human Microbiome Project (HMP), an NIH-led international undertaking that seeks to identify and sequence the vast populations of microbes that live on and within the human body. Some scientists estimate that microbial cells outnumber human cells in a healthy adult by 10 to 1, but few of these fellow travelers have been characterized, and their role in human health largely is a mystery. Many, if not most, of these microbes cannot be grown in a laboratory dish; they are dependent on their natural environment—us. Therefore, to sequence their genomes, HMP researchers will use a new method called metagenomics, which involves sequencing and analysis of genetic material drawn from whole microbial communities in their natural setting.

Among the newer NIH initiatives is the 5-year Human Microbiome Project, an NIH-led international undertaking that seeks to identify and sequence the vast populations of microbes that live on and within the human body.

Initially, the project plans to analyze more than 250 samples from five human body sites—the skin, mouth, airways, gastrointestinal tract, and vagina—and produce a reference set of 1,000 microbial genomes. These will serve as a benchmark against which to compare further sequence data. The project also will test whether metagenomics can be used to link changes in the microbiome with human health.

In one early result from HMP, NIH researchers reported in May 2009 that human skin plays host to an even wider array of bacteria than anticipated.²¹ Drawing on just 20 skin sites from 10 volunteers, the researchers found more than 112,000 bacterial gene sequences representing 19 phyla, 205 genera, and great species diversity. The widest variety of microbes roams the forearm, with 44 species there on average. The least populated site is behind the ear, with 19 species. The major determinant of what bacteria live where seems to be the same factor that governs human real estate prices: location, location, location. Bacteria from any particular body site are more like bacteria from that site in other people than to bacteria elsewhere on the original donor's body. In other words, donor A's mouth bacteria are more like other people's mouth bacteria than they are to bacteria living on donor A's forearm.

Findings such as these will be useful, of course, in developing new treatments for many human diseases. For instance, the study may contribute to efforts to control methicillin-resistant *Staphylococcus aureus* (MRSA), a dangerous bacterium that is resistant to current antibiotics and thus is a growing threat to human health. Scientists had known that many people harbored *S. aureus* in their nostrils; the HMP study detected very similar microbial communities in the crease of skin outside the nose, offering new clues about how the virus is spread, and possibly offering new approaches to preventive measures.

Decoding Cancer

Genomics research has moved the battle against cancer into new, exciting territory. In FY 2008 and FY 2009, GWAS led to the detection of new genes or DNA regions associated with a variety of human cancers. In addition, sequencing of the abnormal DNA within tumors provided new clues about cancer development and potential treatment.

NIH supports a wide variety of such studies, including: the Cancer Genetic Markers of Susceptibility (CGEMS) project, which has been expanded from an initial study of breast and prostate cancer; the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program, which uses genomics in an effort to develop treatments for childhood cancers; and The Cancer Genome Atlas (TCGA), which sequences the DNA within tumors and is being expanded because of the success of its original pilot stage.

Overall, more than 100 genetic variations associated with cancer risk now have been identified. Among the discoveries in FY 2008 and FY 2009 were: a link between pancreatic cancer and the gene that determines ABO blood type;²² identification of a gene that appears to increase the risk of relapse in children treated for acute lymphoblastic leukemia;²³ and variations within several DNA regions that appear to raise the risk of breast,²⁴ colorectal,²⁵ and prostate cancers²⁶—

including, intriguingly, one stretch that contains no genes at all, but that may contain a regulatory sequence that controls a faraway gene (or genes), and may suggest a novel mechanistic pathway of cancer susceptibility shared by a variety of cancers involving this region.

More than 100 genetic variations associated with cancer risk now have been identified.

Sequencing the scrambled DNA within tumors has led to additional discoveries. In one-fourth of melanoma tumors, a gene known as MMP was damaged, indicating that MMP is a tumor suppressor and opening a new approach to treatment of melanoma and other cancers.²⁷ Analysis of glioblastomas (a form of brain tumors) uncovered three disrupted genes and several damaged molecular pathways, suggesting an explanation of why some glioblastomas are resistant to chemotherapy.²⁸ Sequencing of tissue from lung adenocarcinomas, the most common form of lung cancer, detected 26 frequently mutated genes, more than doubling the number of genes linked to the disease.²⁹ Tumor sequencing has proved so fruitful that NIH has plans underway to carry out similar comprehensive analyses of 20 to 25 different cancer subtypes.

The rich lode of data produced by large-scale genomics studies in FY 2008 and FY 2009 may reveal yet more secrets. Much of the raw data is still being analyzed. Moreover, in late 2009, NIH held a workshop involving its own intramural researchers, university researchers, and private-sector officials to discuss the next steps: how to go about combining and analyzing the different data sets being produced, and how to cope with the flood of new data that is being produced as technology improvements make large-scale sequencing faster and cheaper. The advent of massively parallel sequencing technologies has opened an extensive new vista of research possibilities—elucidation of the human microbiome, discovery of polymorphisms and mutations in individual genomes, mapping of protein-DNA interactions, and positioning of nucleosomes—to name just a few. To store, access, and manipulate the enormous volume of read data generated from massively parallel sequencing experiments, NIH has created the Sequence Read Archive, which already contains more than 8,000 billion bases of DNA data.

Revolution in Technology

When the Human Genome Project was first conceived, the cost of sequencing DNA was about \$10 per base pair, and the process was hands-on and painfully slow. If the technology had not been improved and automated, sequencing the genome would have taken more than 100 years and been impossibly expensive. As recently as 2004, the cost of sequencing a person's genome with the then-existing technology would have been about \$20 million. That year, NIH adopted the Advanced DNA Sequencing Technology program and set a target of reducing the cost of sequencing a human genome to about \$100,000 in 2009 and to just \$1,000 in 2014. The goal of a \$100,000 genome was achieved in 2009; the drive toward a \$1,000 genome is on track. That is comparable to the cost of many high-technology medical tests and would make individual genome sequencing tests feasible for hospital patients, ushering in—or at least opening the door to—the era of personalized medicine.

Through the Advanced DNA Sequencing Technology program NIH set a target of reducing the cost of sequencing a human genome. The goal of a \$100,000 genome was achieved in 2009; the drive toward a \$1,000 genome is on track for 2014.

The speed of sequencing also is being dramatically accelerated. Although producing the first full human genome sequence took 13 years and required an international consortium of many laboratories, by 2009 the job could be done in a few weeks on a single sequencing machine. The latest sequencing machines can achieve three times the throughput of the most recent previous platforms, and sequencing capacity is expected to continue growing exponentially. Moreover, the new technologies can detect not just single base changes but also structural variations—rearrangements, duplications, and deletions. The capacity for full genome sequencing is now a possibility for any research laboratory.

A 2009 NIH workshop concluded that these rapid gains in sequencing technology, encouraged and in many cases funded by NIH, will yield a flood of new data to analyze, on top of a data stream that is already testing the limits of current analytic abilities. Improved technology spurs new applications of genomic science. Bioinformatics—that is, computational biology methods, resources, and infrastructure—is a critical tool for the understanding of this wealth of data.³⁰ This is a tremendous challenge, and opportunity, for 2010. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.)

We look toward a future where individual genome sequencing will become both commonplace and affordable, and where primary care physicians will routinely consult their patients' genome analyses for predictions of risk, diagnosis, and drug and dosage selections. As we educate the public and the medical community about the significance and limitations of genomic information, it will be possible to apply genomic knowledge to lessen the burden of disease through better screening, diagnostic, therapeutic, and prevention programs. (Also see the section on *Ensuring Responsible Research* in Chapter 3.)

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research

I = Supported through **I**ntramural research

O = **O**ther (e.g., policy, planning, or communication)

COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program

GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct

ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Functional Genomics of Disease

Medical Sequencing: As more is learned about the genetic contributions to disease, DNA sequence information will become even more important for providing medically relevant information to individuals and their health care providers. When it becomes practical to sequence each patient's genome, genetic information will be used to provide more individualized outlooks of disease risk and improve the prevention, diagnosis, and treatment of disease. NHGRI's medical sequencing program, initiated in 2006, aims to drive continued improvement in DNA sequencing technologies and to produce data important to biomedical research. Seven studies currently are underway to identify the genes responsible for several relatively rare disorders and to survey the range of gene variants that contribute to certain common diseases.

- For more information, see <http://www.genome.gov/15014882>
- This example also appears in Chapter 3: *Technology Development*
- (E, I) (NHGRI)

Genomic Medicine: One of the promises of the Human Genome Project is the personalization of medicine. The time rapidly is approaching when health care providers will be able to use information about each person's unique genetic makeup to develop individualized strategies for detecting, treating, and, ultimately, preventing disease. A number of initiatives are underway to explore this area, including the Multiplex Initiative, the Surgeon General's Family History Initiative, and the ClinSeq project. The Multiplex Initiative, a collaboration between NIH researchers, the Group Health Cooperative in Seattle, and the Henry Ford Health System in Detroit, studied the interest levels of healthy young adults in receiving genetic testing for eight common conditions. The purpose was to understand better how patients respond to the results of genetic tests. The U.S. Surgeon General's Family History online tool, created through a collaborative effort

involving the Office of the Surgeon General, NIH, the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, and the Health Resources and Services Administration, allows people to record health conditions that have affected their relatives. The tool uses a three-generation pedigree to organize family health information in a format that people can easily share with their health care providers and other family members. Such information can lead to more proactive strategies for preventing disease and improving health. Finally, NIH researchers and their collaborators are enrolling volunteers in the ClinSeq project, which is piloting large-scale medical sequencing in a clinical setting, with a focus on cardiovascular disease.

- Guttmacher AE, et al. *N Engl J Med* 2004;351(22):2333-6. PMID: 15564550.
- For more information, see <http://www.multiplex.nih.gov>
- For more information, see <http://www.genome.gov/25521052>
- For more information, see <http://www.hhs.gov/familyhistory>
- For more information, see <https://familyhistory.hhs.gov>
- For more information, see <http://www.genome.gov/20519355>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E, I) (NHGRI)

Developmental Genomics: Neural tube defects are a class of birth defects affecting the brain and spinal cord. Taking folic acid during the weeks before and after conception greatly can reduce a woman's chances of having a child with a neural tube defect. Still, researchers have not yet fully defined the complex relationship that exists between folic acid and vitamin B12, which is essential for synthesizing DNA during growth and development. Because Ireland has a particularly high rate of neural tube defects, NIH researchers collaborated with Irish researchers to look more closely at the role of vitamin B12 in the developmental disorder. They found that children born to women who have low blood levels of vitamin B12 shortly before and after conception have an increased risk of a neural tube defect. In light of their discovery, researchers said it would be wise for all women of childbearing age to consume the recommended amount of vitamin B12 in addition to folic acid. In a study looking at a different type of birth defect, a trans-NIH team found that about 20 percent of the incidence of isolated cleft lip may be due to a very tiny alteration in a gene involved in facial development. Oral-facial clefts are among the most common birth defects in the United States, arising from disruptions in a dynamic but still poorly understood interplay of genes, diet, and environment.

- Molloy AM, et al. *Pediatrics* 2009;123(3):917-23. PMID: 19255021.
- Rahimov F, et al. *Nat Genet* 2008 Nov;40(11):1341-7. PMID: 18836445. PMCID: PMC2691688.
- For more information, see <http://www.genome.gov/27530477>
- For more information, see <http://www.genome.gov/27528380>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E, I) (NHGRI, NICHD, NIDCR)

Study Finds Unexpected Bacterial Diversity on Human Skin: One of the NIH Roadmap initiatives, the Human Microbiome Project (HMP) is a trans-NIH program that aims to expand upon traditional microbiology and discover what microbial communities exist in different parts of the human body and how they might change with disease. In a healthy adult, microbial cells far outnumber those of the human host, but remarkably little has been known until now about how these microbes behave in the body. HMP makes use of a metagenomic approach that reveals data about entire human-associated microbial communities. In 2009, data gathered by a trans-NIH team revealed unexpected bacterial diversity on human skin that, it is hoped, will lead to advances in understanding a range of disorders, such as eczema, psoriasis, and acne.

- Grice EA, et al. *Science* 2009;324(5931):1190-2. PMID: 19478181.
- For more information, see <http://nihroadmap.nih.gov/hmp/index.asp>

Genomics

- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (I) (NHGRI, Common Fund - all ICs participate, NCI)

ENCODE: The ENCYclopedia Of DNA Elements (ENCODE) is an international research consortium organized by NIH that seeks to identify all functional elements in the human genome. Until now, most studies have concentrated on the 1 percent of the genome that contains protein-coding genes, overlooking the many other parts of the human genetic blueprint that are important to biological function. ENCODE's exciting discoveries may well reshape the way scientists think about the genome and pave the way for more effective approaches to understanding and improving human health. Efforts to uncover functional elements also extend to some of the organisms most often used in biomedical research. The model organism ENCYclopedia of DNA Elements (modENCODE) Project is analyzing the genomes of the fruit fly, *Drosophila melanogaster*; and the round worm, *Caenorhabditis elegans*. The data that are expected to result from modENCODE project will provide important insights into the biology of these model organisms, as well as provide a valuable tool for comparative studies aimed at understanding human biology.

- For more information, see <http://www.genome.gov/10005107>
- For more information, see <http://www.genome.gov/26524507>
- (E) (NHGRI)

Genetics of Diabetes: Diabetes is a common, potentially deadly and debilitating chronic disease that poses an enormous health care burden. Both of the most common forms of diabetes, type 1 and type 2, are caused by an intersection of genetic and environmental risk factors. Although genetic effects on developing diabetes are profound, they are not simple, as there are many genes that influence the likelihood of developing type 1 or type 2 diabetes. Further, ethnicity impacts both genetic and environmental risk factors. To learn more about diabetes genetics, particularly through new genomic technologies, NIH supports the Type 1 Diabetes Genetics Consortium to study type 1 diabetes, and several major grants to study the genetics of type 2 diabetes. These programs now have identified at least 40 genetic regions linked to type 1 diabetes and at least 38 type 2 diabetes genes. Other studies are refining our understanding of how these genes affect diabetes risk. Many of these projects are geared to collect data from multiple ethnic groups, but a recent initiative sought to advance knowledge of diabetes risk genes in specific racial and ethnic groups disproportionately affected by type 2 diabetes, to understand how different genes affect different populations.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-004.html>
- For more information, see <http://www.t1dgc.org>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
- (E) (NIDDK, NHGRI, NIAID, NICHD)

Advances in Understanding the Genomic Risk for Schizophrenia: Three genome-wide studies have pinpointed a vast array of genetic variation that cumulatively poses the greatest risk for schizophrenia yet reported. All three studies implicate an area of chromosome 6 (6p22.1), which is known to harbor genes involved in immunity and genes that control how and when genes turn on and off. Among sites showing the strongest associations with schizophrenia was a suspect area on chromosome 22 and more than 450 variations in the suspect area on chromosome 6. Individually, these variants' effects statistically were insignificant, but cumulatively they were very powerful. Additionally, one of the studies traced schizophrenia and bipolar disorder, in part, to the same chromosomal neighborhoods. These findings suggest that if some of the same genetic risks underlie schizophrenia and bipolar disorder, then these disorders may originate from a common vulnerability in brain development.

- Shi J, et al. *Nature* 2009;460(7256):753-7. PMID: 19571809. PMCID: PMC2775422.
- Stefansson H, et al. *Nature* 2009;460(7256):744-7. PMID: 19571808.
- International Schizophrenia Consortium, et al. *Nature* 2009;460(7256):748-52. PMID: 19571811.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIMH)

The Collaborative Study on the Genetics of Alcoholism (COGA): In its 20th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) that are densely affected by alcoholism, enabling researchers to take a multigenerational perspective. A recent COGA study focusing on adolescents follows individuals longitudinally as they transition through the age of risk. Investigators have identified several genes, including *GABRA2*, *ADH4*, *ADH5*, *CHRM2*, *GRM8*, *GABRR1*, and *GABRR2* (*Rho 1* and *2*) that influence the risk for alcoholism and related behaviors, such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected, and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes that influence vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

- Xuei X, et al. *Am J Med Genet B Neuropsychiatr Genet* 2009;150B(3):359-68. PMID: 19536785. PMCID: 2829340.
- For more information, see <http://zork.wustl.edu/niaaa>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIAAA) (GPRA)

New Genetics/Epigenetic Tools Shed Light on Addiction: NIH-supported research is taking full advantage of expanding databases and fast technologies to identify links between genetic variations and disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms underlying complex diseases like addiction, which genes strongly influence. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as "gene chips" (e.g., the neurexin gene has been found to play a role in drug addiction). Applying these tools to addiction and other brain disorders advances our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient's genetic profile. To complement these efforts, NIH is investing in the equally important field of epigenetics, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the deleterious long-term changes to brain circuits from drug abuse. For example, using a powerful new technique known as ChIP-on-chip to monitor epigenetic changes correlated with gene activity, investigators recently have mapped the genomic effects of chronic cocaine use in the reward center of the mouse brain. Such analyses provide needed information about which genes are altered by cocaine and can point to new targets for medications development. Epigenetic discoveries also can inform ways to smartly alter environmental factors so as to decrease the risk for drug abuse and addiction.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-015.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-016.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-003.html>

Genomics

- For more information, see <http://nihroadmap.nih.gov/epigenomics/initiatives.asp>
- For more information, see <http://nihroadmap.nih.gov/commonfundupdate.asp>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E/I) (NIDA, NCI, NIAAA, NIMH) (GPRA)

Regulation of Gene Expression by Chemically Marking DNA: Studies by NIH intramural scientists of how genes are turned on (expressed) or off have provided insight into gene regulation and the overall organization of the genome. For example, a recent study indicated the importance of a mammalian protein called Vezf1 in maintaining the integrity of the genome. This protein previously had been identified by research on an "insulator" element—a segment of DNA that marks boundaries in the genome and allows neighboring genes to be regulated independently. Research on insulator elements—found in fruit flies, chickens, and mammals—has provided great insight into the molecular mechanisms used by the cell to turn on certain genes while keeping other genes turned off. In studies of Vezf1, the scientists discovered that deletion of the gene encoding the Vezf1 protein in a mouse embryonic stem cell line led to loss of specific chemical marks on the DNA at widespread sites in the genome. This type of chemical mark, known as DNA methylation, is a signal used by the cell to turn a gene off. The scientists also demonstrated that the loss of DNA methylation observed when Vezf1 was deleted was due to a decrease in the amount of a specific protein that puts this mark on the DNA. Therefore, Vezf1 is required for the DNA methylation pattern in these cells. Continued studies of insulators and their associated proteins will lead to further understanding of the regulation of genes, an essential process for health and development.

- Gowher H, et al. *Genes Dev* 2008;22(15):2075-84. PMID: 18676812. PMCID: PMC2492749.
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (I) (NIDDK)

Genetics of Chronic Kidney Disease: Researchers recently have made progress in uncovering the role of genetics in chronic kidney disease (CKD) arising from various causes. Scientists recently have identified a genetic region that is strongly associated with CKD in African Americans that arises as a consequence of conditions other than diabetes, such as high blood pressure and HIV-associated kidney disease. Several variants associated with the *MYH9* gene were identified as major contributors to excess risk of this kind of CKD among African Americans. This finding suggests that CKD may proceed along different paths depending on whether diabetes or another condition is the underlying disorder. The Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to study progression of an inherited form of kidney disease, polycystic kidney disease (PKD). Phase I of the study demonstrated that magnetic resonance imaging accurately could track structural changes in the kidneys; Phase II showed that patients with mutations in the *PKD1* gene have more cysts and larger kidneys than patients with *PKD2* mutations. A planned third phase of CRISP will provide critical information about the validity of changes in kidney volume as a surrogate marker for loss of kidney function. NIH also has launched a study to identify and validate biomarkers and risk assessment tools for kidney function, injury, and disease progression in patients with CKD, to predict risk, aid early diagnosis, and assess disease progression.

- Kopp JB, et al. *Nat Genet* 2008;40(10):1175-84. PMID: 18794856.
- Kao WHL, et al. *Nat Genet* 2008;40(10):1185-92. PMID: 18794854. PMCID: PMC2614692.
- Grantham JJ, et al. *New Engl J Med* 2006;354(20):2122-30. PMID: 16707749.
- Rule AD, et al. *J Am Soc Nephrol* 2006;17(3):854-62. PMID: 16452494.
- For more information, see <http://www.nih.gov/news/health/sep2008/niddk-14.htm>
- For more information, see <http://www.nih.gov/news/pr/may2006/niddk-17.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
- (E/I) (NIDDK, AHRQ, NCI, NCRR, NHLBI)

Genotyping Information for Use in Warfarin Therapy: The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), a component of the Pharmacogenetics Research Network (PGRN), sponsors data-sharing consortia. In 2009, one of the consortia, the International Warfarin Pharmacogenetics Consortium (IWPC), completed its first project: Clinical and genetic data from more than 4,000 patients worldwide who received warfarin were assembled into a large dataset to create a universal dose algorithm that incorporated genetic factors along with clinical factors. This established a better method to calculate the initial dose of the anticoagulant, and NIH will use the information for a prospective clinical trial to determine the value of pre-prescription genotyping. Further genomic analyses of the warfarin data set are underway. Based upon the success in this endeavor, more consortia were created in 2009. The International Tamoxifen Pharmacogenetics Consortium (ITPC) was formed to gather genetic and clinical data on the efficacy and toxicity of tamoxifen from patients around the world to test for specific associations between genetic variants and clinical effects, and the International Severe Irinotecan Neutropenia Consortium (INSINC) was formed to assemble a large dataset to answer questions definitively relating to genetic effects on adverse outcomes of irinotecan therapy, and to provide tools for evaluating toxicity risk.

- International Warfarin Pharmacogenetics Consortium, et al. *N Engl J Med* 2009;360(8):753-64. PMID: 19228618. PMCID: PMC2722908.
- For more information, see <http://www.nigms.nih.gov/Initiatives/PGRN>
- For more information, see <http://www.pharmgkb.org/views/loadConsortia.action>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIGMS, NCRR, NHLBI, NINDS) (GPRA)

Understanding the Progression from a Skin Disorder to Asthma in Children: NIH-funded researchers investigating basic biochemical mechanisms involved in development have discovered a mechanism that can explain how 50-70 percent of young children affected with the skin rashes of atopic dermatitis (a type of eczema) eventually become asthmatic. The process involves the overproduction of a specific signaling molecule by inflamed skin cells that can trigger the hypersensitivity characteristic of asthma in lung cells. This mechanism and possible ways to prevent this "atopic march" and the development of asthma in general are being actively evaluated in animal models as well as in early human studies.

- For more information, see <http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1000067>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIGMS)

Genetic Epidemiology of COPD (COPDGene): This investigator-initiated research program is performing genetic testing in more than 10,000 current or former smokers to identify genes that are associated with the presence of COPD (chronic obstructive pulmonary disease). In this large and diverse cohort, half of the subjects will be women and one-third will be African American. Although COPD is the fourth most common cause of death in the United States, understanding why some smokers develop serious lung disease and others do not is lacking. Genetics studies may reveal factors that determine this differential susceptibility to disease. The COPDGene study will help to identify individuals at greatest risk, point to particular molecular pathways that may be involved in pathogenesis, and suggest possible targets for prevention and drug therapy. The phenotypic and genetic data generated by the program will be made available through an NIH data repository to allow additional research analyses by other investigators. COPDGene has thus far enrolled more than 4,000 subjects at 17 sites across the United States.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NHLBI)

Genomics

Challenge Program in Integrative Research: Mechanisms of Susceptibility to Oxidative-Stress Disease: This project is an interdisciplinary, collaborative effort to combine the use of simple eukaryotic systems, mouse models, genetic polymorphisms, genomics, clinical research, and patient samples to investigate the mechanisms of susceptibility to the development of oxidative stress-induced disease. The initial phase of the program is focused on bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP), chronic diseases associated with very low birth weight infants. This program consists of three interactive projects: (1) positional cloning of BPD/ROP susceptibility genes in inbred mice; (2) investigating the role of mitochondrial reactive oxygen species in hyperoxia-induced tissue injury; and (3) searching for oxidant susceptibility genes and neonatal diseases in prospective case-parent triad cohorts. Together this group will identify stress response networks, develop and validate early biomarkers of disease, and identify candidate genes and genetic polymorphisms that influence susceptibility to oxidative stress. This program has established a highly collaborative research team uniting bench science with clinical research and patient outcomes. The long-term goal of this program is to understand the role of specific genes that increase human susceptibility to oxidant stress-induced diseases. Thus, this team has the potential to affect a large number of environmentally induced diseases associated with inflammation and reactive oxygen species, including asthma, atherosclerosis, cancer, cardiovascular disorders, and neurodegenerative diseases.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (I) (NIEHS)

Longevity Assurance Gene (LAG) Initiative and Interactive Network: The NIH-supported LAG Initiative has been one of the most successful research initiatives in the field of aging biology and has generated a number of highly significant advances in our understanding of the biological pathways and mechanisms responsible for extension of life span and health span in model organisms. Notably, the LAG initiative has led to the identification of more than 100 new longevity-associated genes, along with many other conserved biological processes and pathways that regulate longevity in a host of divergent species, including humans. Several longevity genes and pathways identified in model organisms as part of the LAG Initiative now are being studied in human populations to determine if analogous genes/pathways are involved in determining human longevity and health span.

- (E) (NIA)

Confronting the Challenge of Antimicrobial Resistance: Antimicrobial resistance has become a major public health threat that is severely jeopardizing the utility of many "first-line" antimicrobial agents. The development of resistance can be caused by many factors, including the inappropriate use of antibiotics. NIH supports a robust basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes. NIH also is pursuing translational and clinical research in this area, including clinical studies to test interventions for community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection and to evaluate the efficacy of off-patent antimicrobial agents. NIH laboratories are at the forefront of understanding the fundamental causes of resistance—from studies of the disease-causing organisms and the progression of disease to research on the advantages and shortcomings of current antibiotics. Specific research foci of NIH researchers and NIH-supported grantees include MRSA and vancomycin-resistant *Staphylococcus aureus* (VRSA) (commonly acquired in community settings), and drug-resistant malaria and tuberculosis. NIH supports genomic sequencing through its Microbial Sequencing Centers; researchers at these centers have sequenced the genomes of numerous disease-causing bacteria, viruses, parasites, and fungi, which may help identify mechanisms of resistance and when and where resistance emerges.

- For more information, see <http://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm>

- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
- (E/I) (**NIAID**) (GPRA)

The Multi-Ethnic Study of Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter epidemiological study of cardiovascular disease (CVD) in 6,914 men and women from 4 ethnic groups—white, African-American, Hispanic, and Chinese—who have been followed for almost 10 years to identify predictors of progression of subclinical CVD. The study originally was funded from 1999 to 2008 and subsequently renewed through 2015. It has measured and compared the predictive value of chest computed tomography, cardiac magnetic resonance imaging, carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for the development of CVD. MESA has major ongoing ancillary studies in the areas of air pollution (funded by the EPA), chronic lung disease, and genetics. MESA SHARe (SNP Health Association Resource) will combine genome-wide scans with detailed phenotypic information and share these data with the scientific community for genome-wide association analyses.

- For more information, see <http://mesa-nhlbi.org>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (**NHLBI**, NEI)

Revolution in Technology

Genome Technology and the \$100,000 and \$1,000 Genome Initiatives: Taking the discoveries made in genetic research initiatives and delivering them to patients on a much wider basis will require significant decreases in the cost and time needed to sequence an entire human genome. Rapid gains have been made on this front since the start of the Human Genome Project and costs continue to fall dramatically. However, it still remains prohibitively expensive to sequence the genomes of individual patients in the clinic. Developing technology to make genome sequencing more affordable is essential for making genomic information part of routine medical care. NIH's Genome Technology program supports research to develop rapid, low-cost methods, technologies, and instruments that will:

- Read DNA sequences
- Check sequences for genetic variations (SNP genotyping)
- Aid research to understand the effects of genetic variations on genomic function.

In 2004, NIH began funding research to develop technologies specifically intended to lower the cost of sequencing the amount of DNA in a human genome, about 3 billion base pairs. These efforts include:

- "Near-Term Development for Genome Sequencing" Grants. These awards support research to enable the sequencing of a human-sized genome for about \$100,000.
- Revolutionary Genome Sequencing Technologies Grants. These awards aim to develop breakthrough technologies that will enable an individual's genome to be sequenced for \$1,000 or less.

- For more information, see <http://www.genome.gov/10000368>
- For more information, see <http://www.genome.gov/27527585>
- This example also appears in Chapter 3: *Technology Development*
- (E) (**NHGRI**)

Genomics

NIH Roadmap Technology Development in Epigenetics: The key focus of the Technology Development in Epigenetics initiative is to foster the development of revolutionary technologies with the potential to significantly change how epigenomics research is performed in the future. Although the technologies and tools for evaluating epigenetic events are improving, existing constraints impede even more rapid progress. Nine grants were funded in 2009 as the result of this initiative. Five of the funded R01 scientists were new investigators. In the future, technological improvements in epigenome-wide mapping and related technologies may enable epigenomic changes to be used to diagnose and investigate the effects of environmental exposures (e.g., drugs of abuse, toxins, infection) on disease (e.g., cancer, neuropsychiatric disorders, aging).

- For more information, see <http://nihroadmap.nih.gov/epigenomics/>
- (E) (NIDA, Common Fund - all ICs participate)

DNA in 3-D: The sequence of the 3 billion DNA base pairs that make up the human genome holds the answers to many questions related to human development, health, and disease. Consequently, much research aimed at understanding the genome has focused on decoding the information conveyed by the linear order of DNA bases. Now, a team that includes an NIH intramural researcher has devised a new way of analyzing functional regions the human genome. The novel approach involves looking at the three-dimensional shape of the genome's DNA, rather than just the base pair sequence. By combining chemical and computer analyses, the researchers survey the landscape, or topography, of DNA structure for areas likely to play a key role in biological function. The method involves identifying all of the grooves, bumps, and turns of the DNA that makes up the human genome and then comparing those structural features to those seen in the genomes of other animal species. Structural features that have been preserved across many species are likely to play important roles in how the human body functions, while those that have changed a great deal over the course of evolution may play a less central role or no role at all.

- Parker SC, et al. *Science* 2009324(5925):389-92. PMID: 19286520. PMCID: PMC2749491.
- For more information, see <http://www.genome.gov/27530624>
- (I) (NHGRI)

Scientists Accomplish Initial Catalogue of the Human Salivary Proteome: Secretions from the major salivary glands (parotid, submandibular, and sublingual) contain many peptides and proteins. They contribute to saliva's important roles in maintaining oral health, including antimicrobial, lubricating, buffering, and digestive properties. Salivary gland disorders, which result in severe dry mouth, compromise quality of life because they often lead to decay and periodontal diseases, mucosal infections, halitosis, taste impairment, and difficulties in swallowing and speaking. Saliva is a complex fluid; over the years, a number of salivary proteins have been reported but a systematic approach to catalogue all the proteins present in saliva was only initiated in 2004. NIH supported three teams of investigators to conduct the first comprehensive analysis of the salivary proteome. After samples were collected and analyzed, the data were standardized and integrated, yielding a salivary proteome that comprises 1,166 proteins. Of these proteins, 152 parotid and 139 submandibular/sublingual proteins were identified by all three research groups; these proteins form the core proteome. Most proteins identified were extracellular or secretory proteins, and involved in numerous molecular and cellular processes. A significant number of proteins represented in the salivary proteome also have been found to exist in the plasma or tear proteomes. This initial catalogue of the salivary proteome is a significant first step toward a comprehensive understanding of what the functions of saliva are, and how salivary composition is dependent on physiological variations, including on health and disease. This proteome could be the source of potential diagnostic and prognostic biomarkers for oral and systemic conditions.

- Denny P, et al. *J Proteome Res* 2008;7:1994-2006. PMID: 18361515.

- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E) (NIDCR)

Increased Efficiency for Genetic Engineering Research Methods: Gene therapy—the ability to cure a genetic disease by replacing or destroying the faulty copy of a gene—has been limited by the difficulty of designing chemical "bullets" that will zap the defective gene without affecting any of the other genes in a person's cells. Recently, NIH-supported researchers have developed a method, called OPEN, for creating gene-specific chemical bullets that is much faster, easier, and cheaper than alternative technologies. OPEN has the potential to revolutionize genetic engineering, and it will also greatly enhance the progress of genetic research in all organisms.

- Maeder M, et al. *Mol Cell* 2008;31(2):294-301. PMID: 18657511. PMCID: PMC2535758.
- (E) (NIGMS)

The Big Picture: Genome-Wide Association Studies

Genome-Wide Association Studies: With unprecedented speed, researchers have used an approach called genome-wide association studies (GWAS) to explore genetic variants and their complex relationships to human health and disease. GWAS research has linked a stunning number of genetic variants to common conditions—more than 130 in 2008 alone. For example, the obesity epidemic and its related health conditions pose a great challenge for the Nation. In 2008, the Genetic Investigation of Anthropometric Traits consortium identified six genes associated with body mass index, a key indicator for obesity. Also in 2008, three GWAS of lung cancer implicated several genes already known to be linked to nicotine addiction. In a feat that would not have been possible without the power of whole genome analysis, the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium in 2009 gathered data from participants in long-running studies to reveal genetic variants associated with an increased risk of stroke. Identification of genetic variants associated with common diseases opens new windows into the biology of health and disease. This work also raises the possibility of someday using genetic testing, in combination with family history, to identify at-risk, pre-symptomatic individuals who might benefit from personalized screening and preventive therapies.

- For more information, see <http://www.genome.gov/27528559>
- For more information, see <http://www.genome.gov/27529231>
- For more information, see <http://www.genome.gov/27531390>
- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E, I) (NHGRI, NIDDK, NCI, NIA, NHLBI, NIMH, NINDS)

Population Genomics, GAIN, and GEI: In 2006, HHS announced the creation of two groundbreaking initiatives for population genomics research in which NIH played a leading role. The Genetic Association Information Network (GAIN) was a public-private partnership involving NIH, the Foundation for NIH, Pfizer, Affymetrix, Perlegen, the Broad Institute, and Abbott. GAIN supported a series of genome-wide association studies designed to identify specific points of DNA variation associated with the occurrence of common diseases. Investigators from existing clinical studies were invited to submit samples and data on roughly 2,000 participants for genomic assays designed to capture roughly 80 percent of the common changes in the human genome. GAIN successfully concluded in November 2008, with the third and final public workshop on the project. At this meeting, investigators from across the research community shared their findings and discussed how they had used the data generated through GAIN in their own research. Data from the GAIN studies have been deposited into the NIH database of Genotype and Phenotype (dbGaP) for the broad use of the research community. Access is controlled by the GAIN Data Access Committee. Additionally, NIH funds the Genes, Environment, and Health Initiative (GEI), an NIH-wide effort combining comprehensive genetic analysis and environmental technology

development to understand the causes of common diseases. GEI has held a number of workshops to identify novel ways of analyzing the wealth of information gathered and to use that data to improve human health.

- For more information, see <http://www.genome.gov/19518664>
- For more information, see <http://www.genome.gov/19518663>
- For more information, see <http://genesandenvironment.nih.gov>
- For more information, see <http://www.genome.gov/11511175>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E, I) (NHGRI, NIEHS, NLM)

Genome-Wide Association Studies of Autoimmune Disease Risk: In recent years, genome-wide association studies (GWAS) have transformed the identification of gene regions related to disease risk, through an unbiased analysis of patients with a disease, in comparison with people who don't have it. These GWAS require large numbers of patients and individuals without the disease to obtain statistically significant results. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects, in addition to productive, multisite collaborations across the United States, including international researchers and contributions from the NIH Intramural Research Program. GWAS have yielded important information about disease risk, as well as understanding of disease pathways and potential therapeutic targets, in several autoimmune diseases in the past 2 years. Diseases studied include psoriasis, rheumatoid arthritis, systemic lupus erythematosus (or lupus), ankylosing spondylitis, and type 1 diabetes. Initial results from GWAS require confirmation by replication in additional groups of patients. More detailed localization of disease risk genes can be achieved through comprehensive DNA sequencing of candidate gene regions. New NIH initiatives are supporting these follow-up studies, which are critical to validating GWAS findings.

- Plenge RM, et al. *Nat Genet* 2007;39(12):1477-82. PMID: 17982456. PMCID: PMC2652744.
- Wellcome Trust Case Control Consortium, et al. *Nat Genet* 2007;39(11):1329-37. PMID: 17952073. PMCID: PMC2680141.
- Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
- Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
- Liu Y, et al. *PLoS Genet* 2008;4(3):e1000041. PMID: 18369459. PMCID: PMC2274885.
- Nair RP, et al. *Nat Genet* 2009;41(2):199-204. PMID: 19169254. PMCID: PMC2745122.
- Barrett JC, et al. *Nat Genet* 2009;41:703-707. PMID: 19430480. PMCID: PMC2889014.
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/10_04.asp
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-09-135.html>
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2008/Ankyl_Spond_gene.asp
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-123.html>
- For more information, see <http://www.nature.com/ng/journal/v41/n6/abs/ng.381.html>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (NIAMS, NCRR, NHGRI, NHLBI, NIAID, NICHD, NIDA, NIDCR, NIDDK)

Lupus: There have been significant advances in identifying disease risk genes for systemic lupus erythematosus (lupus) in recent years. Genome-wide association, linkage analysis, and direct sequencing have revealed genetic variations in lupus patients for molecules involved in immune mechanisms and regulation, inflammation, and vascular cell activities. The disease affects women disproportionately, with female lupus patients outnumbering males nine to one. African American women are three times as likely to get lupus as Caucasian women, and it also is common more in Hispanic, Asian, and American Indian women. These results are being replicated in distinct racial and ethnic populations. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects. Another critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by

government agencies, private foundations, and industry. The numerous genes uncovered in these studies reflect the complex expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene specifically is associated with severe forms of lupus that include kidney disease, but not skin manifestations. Methods to analyze patients' blood samples are being developed to group disease-specific variations in gene expression according to pathogenic mechanisms. This system may be used to predict flares of lupus activity in the future and guide individualized treatment. Lupus risk genes also have been discovered on the X chromosome and reproduced in animal models of the disease. These important findings shed light on the female predominance of lupus.

- Edberg JC, et al. *Hum Mol Genet* 2008 Apr 15;17(8):1147-55. PMID: 18182444.
- Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
- Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
- International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), et al. *Nat Genet* 2008;40(2):204-10. PMID: 18204446.
- Taylor KE, et al. *PLoS Genet* 2008;4(5):e1000084. PMID: 18516230. PMCID: PMC2377340.
- Chaussabel D, et al. *Immunity* 2008;29(1):150-64. PMID: 18631455. PMCID: PMC2727981.
- Smith-Bouvier DL, et al. *J Exp Med* 2008;205(5):1099-108. PMID: 18443225. PMCID: PMC2373842.
- Scofield RH, et al. *Arthritis Rheum* 2008;58(8):2511-7. PMID: 18668569.
- Jacob CO, et al. *Proc Natl Acad Sci U S A* 2009;106(15):6256-61. PMID: 19329491. PMCID: PMC2669395.
- This example also appears in Chapter 2: *Autoimmune Diseases*, Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NIAMS, NCI, NCR, NHLBI, NIAID, NIDCR, NINDS)

Psoriasis: Early studies of families of psoriasis patients indicated a genetic susceptibility for the disease. Genome-wide association studies (GWAS) have revealed genetic variations in psoriasis patients for previously identified immune system proteins. New disease risk genes, which are associated with inflammation and immune function, also have been found. Some of these variations occur in or near gene regions associated with other autoimmune diseases, such as rheumatoid arthritis, lupus, and Crohn's disease, although in distinctly independent genes. In addition to variations in genes associated with immune function, GWAS have uncovered differences among psoriasis patients in genes involved with skin differentiation and regulation of inflammation.

- Liu Y, et al. *PLoS Genet* 2008;4(3):e1000041. PMID: 18369459. PMCID: PMC2274885.
- Nair RP, et al. *Nat Genet* 2009;41(2):199-204. PMID: 19169254. PMCID: PMC2745122.
- This example also appears in Chapter 2: *Autoimmune Diseases*
- (E) (NIAMS, NIDA)

Seeking Solutions for People with Sjogren's Syndrome: Sjogren's syndrome is one of the most prevalent autoimmune disorders, affecting as many as 4 million people in the United States. Nine out of 10 patients affected are female. It is an autoimmune disease that progressively destroys salivary and lachrymal glands. The most common symptoms include dry eyes, dry mouth, fatigue, and musculoskeletal pain. A significant roadblock for moving discoveries ahead in the field of Sjogren's syndrome is the lack of data and biospecimens available for research. Recognizing the problem, NIH spearheaded an effort to establish Sjogren's patient registries at two extramural institutions as well as through its own intramural program. These groups are working together to generate and share with the general research community the genome-wide genotyping data and clinical information from the cohorts enrolled through these efforts. This resource should jumpstart efforts to understand genetic contributions to Sjogren's syndrome and the etiologic overlap with related autoimmune conditions such as lupus and rheumatoid arthritis. In addition to participating in the patient registry and genotyping efforts described above, the Sjogren's Syndrome Clinic, located in the NIH CC, collects systematic clinical and laboratory data on the Sjogren's syndrome (and salivary dysfunction) population. Gene therapy and bioengineering hold promise for the repair or even replacement of salivary glands ravaged by Sjogren's syndrome. More than 300 patient visits

Genomics

occur annually, and the clinic is expanding its patient recruitment to accelerate the conduct of clinical trials that might shed light on this disorder.

- Korman BD, et al. *Genes Immun* 2008;9(3):267-70. PMID: 18273036.
- Roescher N, et al. *Oral Dis* 2009;15(8):519-26. PMID: 19519622. PMCID: PMC2762015.
- Nikolov NP, Illei GG. *Curr Opin Rheumatol* 2009;21(5):465-70. PMID: 19568172. PMCID: PMC2766246.
- For more information, see <http://www.sjogrens.org/>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (NIDCR, CC, ORWH)

SNP-Health Association Resource (SHARe): SHARe conducts genome-wide association studies in several large NIH cohort studies to identify genes underlying cardiovascular and lung diseases and other disorders such as obesity and diabetes. The resulting genotype data along with the cohort phenotype data are made available to researchers around the world through the NIH dbGAP database. Framingham SHARe, with 9,000 participants, was the first cohort released in this initiative due to its uniqueness in including 3 generations of participants with comparable data obtained from each generation at the same age. As of October 31, 2009, 95 projects to use these data had been approved. A modified version of the dataset was distributed to 72 approved research projects as the focus of a Southwest Foundation Genetic Analysis Workshop. The second cohort released was the SHARe Asthma Resource Project, which includes genotype data from more than 2,500 adults and children who have participated in NIH clinical research trials on asthma. As of October 31, 2009, 11 projects to use these data had been approved. Data from more than 12,000 African-American and Hispanic women from the Women's Health Initiative and approximately 8,300 participants from the Multi-Ethnic Study of Atherosclerosis were released in January 2010.

- For more information, see <http://www.nih.gov/news/pr/oct2007/nhlbi-01.htm>
- For more information, see <http://nih.gov/news/health/dec2008/nhlbi-15.htm>
- For more information, see <http://view.ncbi.nlm.nih.gov/dbgap/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NHLBI, NLM)

Unraveling the Complexity of the Genetics of Glaucoma: Glaucoma is a group of eye disorders that share a distinct type of optic nerve damage, which can lead to blindness. It is the leading cause of blindness in African Americans. More than 2 million Americans have been diagnosed with glaucoma, and the prevalence of the disease will rise to a projected 3 million by 2020. Glaucoma research aims to understand the complex genetic factors that lead to common forms of the disease and to develop treatments that protect ganglion cells of the retina from the damage that leads to vision loss. Under GPRA, NIH set a goal by 2012 to identify the genes that control the risk of glaucoma. To achieve this goal, NIH launched a large genome-wide association study to identify glaucoma risk genes. NEIGHBOR (NEI Glaucoma Human Genetics CollaBORation) is a unique collaborative effort involving 22 investigators at 12 institutions throughout the United States. Approximately 2,000 cases and 2,000 age, sex, and ethnically matched controls will have their complete genome sequenced (genotyped) for a genome-wide association study to identify genetic variants associated with the disease. Genetic data and associated disease characteristics collected from NEIGHBOR will be made available to the research community through the NIH database of Genotypes and Phenotypes (dbGaP).

- Friedman DS, et al. *Arch Ophthalmol* 2004;122(4):532-8. PMID: 15078671.
- For more information, see <http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/about.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NEI, NLM) (GPRA)

Decoding Cancer

Genomic Research on Tumor Cells: In addition to supporting The Cancer Genome Atlas with NCI, NHGRI operates a number of other cancer-focused research programs, both intramural and extramural. The Tumor Sequencing Project (TSP) is a multicenter effort to characterize the genomic changes that occur in lung adenocarcinoma, the most common type of lung cancer in the United States. In 2008, TSP researchers identified 26 genes that often are mutated in these lung tumors, more than doubling the list previously known to scientists and clinicians. In other efforts, a team of NHGRI intramural and NHGRI-funded researchers recently identified an inherited gene alteration linked to increased susceptibility to lung cancer. With further investigation, the researchers said it may be possible to use this genetic information to identify high-risk people who could benefit from earlier, more aggressive screening for lung cancer, in much the same way as women who inherit *BRCA1* and *BRCA2* breast cancer genes may benefit from early mammography and other tests. Other NHGRI work has focused on the most deadly type of skin cancer, melanoma. In 2009, an NHGRI intramural researcher discovered a gene that acts as a tumor suppressor in melanoma. This finding is significant because researchers previously thought drugs that blocked that gene or its protein might offer a new way to treat melanoma, when, in fact, a better strategy might be to activate the gene.

- For more information, see <http://genome.gov/27528559>
- For more information, see <http://healthnews.uc.edu/news/?/8427/>
- For more information, see <http://genome.gov/27530882>
- (E, I) (NHGRI, NCI)

Genome-Wide Association Studies of Cancer Risk: The Cancer Genetic Markers of Susceptibility (CGEMS) project is a signature initiative that uses genome-wide association studies (GWAS) to identify genetic variants and mechanisms associated with cancer risk. Understanding these variants and mechanisms may lead to new preventive, diagnostic, and therapeutic interventions. CGEMS investigators have pinpointed genetic variants associated with elevated prostate cancer risk as well as variants associated with increased breast cancer risk. The same genetic variant was shown to be involved in increased prostate, colon, and other cancers, suggesting a common mechanistic pathway for susceptibility to a variety of cancers. Another GWAS project, the Cohort Consortium, is a unique extramural/intramural collaboration that allows Consortium partners to share access to data on 37 cohorts comprised of 4 million people from diverse populations. Each cohort contains extensive information on known or suspected risk factors and biospecimens collected pre- and post-diagnosis. The large number of study subjects permits the detection of modest genetic effects, as well as studies of variants involved in less common cancers. One cohort within the Consortium, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort, includes about 2.9 million specimens. These pre-diagnostic specimens provide a valuable resource for studies of cancer etiology and early detection. Researchers can correlate changes in molecular profiles associated with the onset of different types of disease, thereby providing valuable insights into the actual mechanisms of human carcinogenesis.

- For more information, see <http://cgems.cancer.gov>
- For more information, see <http://epi.grants.cancer.gov/Consortia/cohort.html>
- For more information, see <http://www.parplco.org>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E/I) (NCI)

Research Tools for Genomic Studies of Cancer: The Cancer Genome Atlas (TCGA) is developing a publicly accessible, comprehensive catalog of the many genetic changes that occur in cancers. Tumor and matched normal samples are analyzed for genetic changes such as chromosome rearrangements and gene mutations; gene expression changes, including changes in expression patterns of microRNAs, as well as epigenetic modifications (differences in the chemical modifications of DNA that influence gene expression). All data, including pre-publication data, are freely available through the TCGA website and are compatible with the cancer Bioinformatics Grid (caBIG®). The first TCGA project,

Genomics

which focused on brain cancer (glioblastoma multiforme), demonstrated the feasibility and impact of large-scale NIH-coordinated cancer genome analysis. Comprehensive characterization of ovarian cancer with other tumor types will follow. The goal of the Cancer Genome Anatomy Project (CGAP) is to provide cancer researchers with tools, resources, and information derived from studies that are characterizing differences between cancer and normal cells. The CGAP website provides access to data, bioinformatic tools, and information about available full-length cDNAs and short hairpin RNA clones. These resources are helping scientists conduct the research necessary to improve detection, diagnosis, and treatment of cancer. In the past year, new projects that explore molecular characterization through novel technologies were added as part of the Cancer Genomic Technology Initiative (CGTI). REMBRANDT is the national portal for molecular, genetic, and clinical data associated with several thousand primary brain tumors. This framework provides researchers the ability to answer basic questions related to a patient or patient populations and view integrated datasets in a variety of contexts.

- For more information, see <http://cancergenome.nih.gov/index.asp>
- For more information, see <http://cgap.nci.nih.gov/>
- For more information, see <https://caintegrator.nci.nih.gov/rembrandt/>
- For more information, see http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm
- This example also appears in Chapter 2: *Cancer*
- (E/I) (NCI, NHGRI, NINDS) (ARRA)

Ethical, Legal, Social and Behavioral Issues

NIH Revision Awards for Studying Interactions Among Social, Behavioral, and Genetic Factors in Health: NIH issued three program announcements with review (PARs) to support competitive supplements for NIH grantees to study how interactions among genetic and behavioral/social factors influence health and disease. NIH is committing \$7.9 million to support 11 applications submitted in response to these announcements, which will enable the addition of a genetics/genomics component to ongoing behavioral or social science research projects. The knowledge gained by such research will improve our understanding of the determinants of disease as well as inform efforts to reduce health risks and provide treatment.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/par-08-065.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-066.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-067.html>
- For more information, see http://obssr.od.nih.gov/scientific_areas/Genes_Beh_Environ/index.aspx
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (OBSSR, NCCAM, NCI, NEI, NHGRI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIMH, NINDS, NINR, ODP/ODS)

Nonhuman Genomes

Microbial Genomics: NIH has made significant investments in large-scale, whole-genome sequencing of pathogens over the last decade. NIH also provides comprehensive genomic, bioinformatic, and proteomic resources and reagents to the scientific community:

- The NIH Genome Sequencing Centers of Infectious Diseases rapidly produce high-quality genome sequences of human pathogens and invertebrate vectors of diseases. Over the last decade, NIH has supported large-scale, whole-genome sequencing of pathogens and vectors. Thousands of bacteria, fungi, parasites, invertebrate vectors of diseases, and viruses have been sequenced, including pathogens that cause anthrax, influenza, aspergillosis, TB, gonorrhea, chlamydia, and cholera. For example, more than 3,733 human and avian influenza isolates have been sequenced including almost 500 for H1N1 (as of December 2009).

- The Pathogen Functional Genomics Resource Center generates and distributes genomic data sets, reagents, resources, bioinformatic analysis tools, and technologies for functional analysis of pathogens and vectors.
- Clinical Proteomics Centers for Infectious Diseases and Biodefense apply state-of-the-art proteomics technologies for the discovery, quantification, and verification of protein biomarkers in infectious diseases. These data are released to the scientific community and may aid in the production of vaccines, diagnostics, and therapeutics.
- Systems Biology Centers for Infectious Diseases bring together a diverse group of scientists to analyze, identify, quantify, model, and predict the overall dynamics of microbial organisms' molecular networks and their host interactions using both computational and experimental methodologies.

- For more information, see <http://www3.niaid.nih.gov/topics/pathogenGenomics/default.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E/I) (NIAID)

Comparative Genomics: One of the primary objectives of today's biomedical research is to define and understand how the human genome functions, how malfunction leads to disease, and how that knowledge can be used to develop new preventive strategies, diagnostic methods, and therapies. Comparison of the genome sequence of humans with those of other organisms identifies regions of similarity and difference, providing insight into the evolution, structure, and function of human genes and pointing to new pathways to combat human disease. Currently, the genome sequences of 197 organisms are either in the pipeline or have been completed through NHGRI funding. Ongoing sequencing targets include mammals, fungi, multiple strains of yeast, and additional nonhuman primates. NHGRI funds this work by supporting three large-scale sequencing centers that are world-renowned for their cost-effective, high-quality work. Recent highlights of this sequencing program include the publication of the genome of domestic cattle, the first livestock mammal to have its genetic blueprint sequenced and analyzed.

- Bovine Genome Sequencing and Analysis Consortium, et al. *Science* 2009;324(5926):522-8. PMID: 19390049.
- For more information, see <http://www.genome.gov/10001691>
- (E) (NHGRI)

Resources

NIMH Center for Collaborative Genetic Studies: Over the last decade, NIH has built the infrastructure for large-scale genetic studies by creating the NIMH Center for Collaborative Genetic Studies (CCGC), a repository of DNA, cell cultures, and clinical data that serves as a national resource for researchers studying the genetics of complex mental disorders. In FY 2008, NIH launched a number of initiatives to enrich the repository through the collection of new biomaterials and clinical data from large cohorts. The CCGC will be enhanced through the creation of a genomic cyberinfrastructure that will integrate and manage data to accelerate genetic analyses. NIH also issued a RFA to encourage studies that will tease apart the complex genetic components of mental disorders, using resources within the CCGC. Projects will study the relationship between genes and illness-specific characteristics, interactions between multiple vulnerability genes, and the role of environmental and experiential influences on gene expression. Through these collective efforts, this research may give us the tools to predict vulnerability, validate diagnosis, and identify targets for new, effective, and personalized mental health treatments.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-130.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-131.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-120.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-121.html>
- For more information, see <http://nimhgenetics.org/>
- (E) (NIMH)

Genomics

Genetic and Genomic Resources for Emerging Non-Mammalian Model Organisms: In FYs 2008 and 2009, NIH funded 13 grants that create genetic and genomic resources for model organisms whose genomes recently have been sequenced. These organisms include fish, invertebrates, and microbes used to understand human health, development, and disease. The resources include reagents and mutant lines, a center for high-throughput mutagenesis, genetic maps, databases, and stock centers.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-457.html>
- (E) (NIGMS)

Reference Epigenome Mapping Centers: The Reference Epigenome Mapping Centers (REMCs), one of the Roadmap Epigenomics initiatives, are developing resources in reference epigenomes that the field has been requesting for the last 5 years, as indicated by recommendations made at several workshops and conferences focused on epigenetics and human health and disease. The funded centers form a network collaborating to provide comprehensive maps of all known epigenetic marks across a set of mutually agreed-upon reference cell types. This consortium, with input from advisors, will identify the most appropriate cell populations and determine standardized methods for growing or acquiring the cells so that data can be compared and integrated maps can be generated. The network of REMCs will produce comprehensive, high resolution, experimental data on epigenetic marks in specific cell populations, such as high-quality, pluripotent human embryonic stem cells, other human differentiating stem cells, and differentiated cell types including human cell types relevant to complex diseases of high public health significance. In addition, it will provide an informatics pipeline to generate high-quality reference epigenome maps from the centers' data; facilitate additional data analyses, in collaboration with the Epigenome Data Analysis and Coordinating Center, to integrate data from maps generated by REMCs from a specific cell type for different epigenetic marks; and conduct ancillary studies to develop limited data on functional aspects of epigenetic control of gene activity.

- For more information, see <http://nihroadmap.nih.gov/epigenomics/>
- For more information, see <http://cancerres.aacrjournals.org/cgi/reprint/65/24/11241>
- For more information, see <http://www.landesbioscience.com/journals/epigenetics/article/heindeleEPI1-1.pdf>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIEHS, NIDA, Common Fund - all ICs participate)

Discovery of Novel Epigenetic Marks in Mammalian Cells: The NIH Roadmap Epigenomics Program aims to accelerate the promise of epigenetics into applications that affect human health and a wide range of common complex human diseases by fostering the development of novel resources for research in this field. Epigenetics refers to various modifications to DNA, its associated proteins, or overall chromosome structure that influence whether genes are active or silent, independent of the DNA sequence. Research supported by this program will characterize the "epigenome," a catalog of the stable epigenetic modifications or "marks" that occur in the genome (and which may differ in different types of cells) and its impact on health and disease. One component of the program is an initiative to support research to identify novel epigenetic marks in mammalian cells and assess their role in the regulation of gene activity. It is anticipated that the results of these studies will be translated quickly to global epigenome mapping in human cells (conducted by the Epigenomics Roadmap Program's Reference Epigenome Mapping Centers). The eight research grants funded by this component of the program are expected to yield results that could have a significant impact on our understanding of gene regulation in mammals. In the long term, advances in these areas will enhance our ability to investigate, diagnose, and ameliorate human disease with a significant epigenetic component. For instance, NIH plans to build on these studies to examine the role of epigenomics in diabetes complications and to study effects of the intrauterine environment on the development of diabetes. Other research will examine epigenetic markers of beta cell differentiation.

- For more information, see <http://nihroadmap.nih.gov/epigenomics/initiatives.asp>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDDK, Common Fund - all ICs participate)

Rodent Model Resources for Translational Research: Mouse and rat models are the primary testbed for preclinical research and have played a vital role in most medical advances in the last century. Rodent models comprise about 90 percent of all animal studies, enabling a wide range of genetic and physiological research on human disease. NIH plays a major role in supporting the availability of normal and mutant mice and rats for translational research. Recent accomplishments include:

- *Knockout Mouse Project (KOMP)*—A trans-NIH initiative to individually inactivate approximately 8,500 protein-coding mouse genes to better understand their genetic functions, which are, in many cases, very similar to human genes. High throughput production started in 2006, and international distribution of validated embryonic stem cell lines with specific knockouts from the KOMP Repository became fully operational in 2008. The KOMP is supported by 19 ICs and Offices.
- *Mutant Mouse Regional Resource Centers*—More than 1,700 mutant mouse lines, and 27,000 mutant embryonic cell lines, are available from the consortium, which comprises three centers across the United States.
- *Rat Resource and Research Center*—Acquisition and distribution of rat models increased dramatically in FY 2008, because of adaptation of novel technologies to make directed mutations.

- For more information, see <http://www.genome.gov/17515708>
- For more information, see <http://komp.org>
- For more information, see <http://www.nih.gov/science/models/mouse/knockout/komp.html>
- For more information, see <http://www.mmrrc.org/>
- For more information, see <http://www.nrrrc.missouri.edu>
- For more information, see http://www.ncrr.nih.gov/comparative_medicine/resource_directory/rodents.asp
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NCRR, NHGRI, NIDA, NINDS)

Database of Genotype and Phenotype (dbGaP): Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics, and other scientific data, NIH established dbGaP to house the results of genome-wide association studies (GWAS), which examine genetic data of de-identified subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2009, dbGaP included results from more than 40 GWAS, including genetic analyses related to such diseases as Parkinson's disease, ALS, diabetes, alcoholism, lung cancer, and Alzheimer's disease. dbGaP is the central repository for many NIH-funded GWAS to provide for rapid and widespread distribution of such data to researchers and accelerate the understanding of how genes affect the susceptibility to and severity of disease.

- For more information, see <http://view.ncbi.nlm.nih.gov/dbgap>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (NLM)

Ethical, Legal, and Social Implications (ELSI) Centers of Excellence: NHGRI's ELSI program has established a network of Centers of Excellence in ELSI Research. Currently, four full Centers and three exploratory Centers are bringing together investigators of diverse expertise to investigate issues related to:

- Intellectual property of genetic information
- Translation of genetic information to health care
- Genetic research that involves human participants
- Use of genetic information and technologies in non-health care settings, such as employment, insurance, education, criminal justice, or civil litigation
- Impact of genomics on the concepts of race, ethnicity, and individual and/or group identity
- Implications of uncovering genomic contributions to human traits and behaviors, such as aging or addictions
- How different individuals, cultures, and religious traditions view the ethical boundaries for the uses of genomics

→ For more information, see <http://www.genome.gov/10001618>

→ This example also appears in Chapter 3: *Clinical and Translational Research*

→ (E) (NHGRI)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects adipose tissue and alters hormonal control of sexual maturation. Endocrine disruptors, irradiation, and psychosocial elements also will be studied for effects.

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→ For more information, see <http://www.bccrc.org/>

→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*

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- ³⁰ Also see the section on Disease Registries, Databases, and Biomedical Information Systems in Chapter 3.

Molecular Biology and Basic Research

*Who would have predicted that curiosity about a naturally glowing protein in the luminescent jellyfish *Aequorea victoria* would lead to the development of a tool that has transformed molecular and cellular biology? The 2008 Nobel Prize in Chemistry was awarded to Drs. Osamu Shimomura, Martin Chalfie, and Roger Tsien for the discovery and development of the green fluorescent protein (GFP). When attached to cellular molecules, GFP allows scientists to peer into living cells and observe molecular processes and cellular development. As is often the case with basic research studies, the yield on the initial research investment was not fully realized for many years. Dr. Shimomura first isolated GFP in 1962, yet it was not until more than 30 years later that Dr. Chalfie demonstrated that GFP could be used as a tag to observe biological processes in the bacteria *E. coli* and the simple roundworm *C. elegans*. Dr. Tsien, who studied the chemical basis of green fluorescence, has created a colorful palette of fluorescent proteins that have been used in exquisitely detailed cell biology studies. With GFP-based studies continuing to generate advances in biomedical research, the discovery and development of GFP have made a significant contribution to our understanding of fundamental biological processes underlying health and disease.*

Introduction

Basic research is a major force driving progress across the biomedical and behavioral sciences and is paramount in uncovering the fundamental principles of biology, wellness, disease, and public health. Investments in basic biomedical and behavioral research make it possible to understand the causes of disease onset and progression, design preventive interventions, develop better diagnostic tests, and discover new treatments and cures. From the incremental advances in our understanding of a given disease to the groundbreaking discoveries that revolutionize our approaches for treating or preventing it, investments in basic research have and will continue to yield inestimable rewards and benefits to public health. As such, fostering a broad basic research portfolio is a critical component of fulfilling the NIH mission.

Uncovering Fundamental Aspects of Biology and Behavior through Basic Research

Biological function occurs over a huge span of spatial dimensions that ranges from organisms to cells to molecules. Despite the range in size, from meters to one-billionth of a meter—which is like comparing the diameter of the earth to the diameter of a marble—similar principles of structure, interaction, and dynamics govern biological function at the molecular, cellular, and organismal levels. These principles have been finely tuned to allow biological processes to play out in concerted harmony; however, disharmony can occur in molecular and cellular structures, interactions, and dynamics that often form the underlying basis of disease.

As examples of fundamental aspects of biology at the molecular level, scientists are interested in understanding how biological macromolecules—proteins, nucleic acids, sugars, and lipids—carry out cellular processes. What molecules are involved and what are their functions? How do their shapes define their functions? How do particular molecules interact to turn their functions on and off? And, how are innumerable molecular events properly coordinated to turn genes on and off, initiate cell growth and division, determine cell type, metabolize nutrients, and, when necessary, instruct a cell to die? Understanding how these events occur in wellness provides a framework for pinpointing molecular causes of disease.

At the cellular level, similar molecular questions are focused on understanding how cells sense and respond to their environment. How do cells interact and communicate with each other to form tissues and the organ structures of our body? How do cells process and distribute nutrients to disparate parts of the body? How do cells orchestrate a response to protect our body from invasion by foreign molecules? What is the molecular program that develops an initial ball of unspecialized cells into a fully functioning human being?

Similar to basic molecular and cellular biomedical research, basic behavioral research does not focus specifically on disease outcomes per se. Rather, it is designed primarily to elucidate knowledge about underlying mechanisms and

processes, knowledge that is fundamental to improving the understanding, explanation, observation, prediction, prevention, and management of illnesses, as well as the promotion of optimal health and well-being. Basic behavioral and social sciences research involves both human and animal studies, as well as many non-animal model systems, and spans the full range of scientific inquiry, from processes involved in the behavior of individuals, as individuals, to those involved in the interactions between and among individuals that explain inter-individual, group, organizational, community, population, macroeconomic, and other systems-level patterns of collective behavior. The domains and units of analysis can include intra-organismic as well as inter-organismic factors ("cells to society"), over varying units of time from nanoseconds to centuries, and lifespan developmental phases and phenomena that may occur within and across generations.

Basic Research Questions are Addressed through an Interdisciplinary Approach

The breadth of basic research questions spans all aspects of human development, physiology, behavior, and disease. Thus, basic research is encompassed in the missions of all NIH ICs. Progress in the basic sciences often requires interdisciplinary approaches. Expertise from multiple disciplines often is needed to develop new technologies, improve methods of data analysis, and provide insight on a fundamental disease pathway. NIH fosters collaborations that span all of the traditional and emerging disciplines of the life, physical, engineering, computer, behavioral, and social sciences.

The breadth of basic research questions spans all aspects of human development, physiology, behavior, and disease. Thus, basic research is encompassed in the missions of all NIH Institutes and Centers.

Although basic research is concerned with advancing our understanding of human health and disease, there are a number of reasons—both ethical and practical—that make humans poor subjects for exploring the fundamental aspects of biology. Therefore, scientists often carry out their basic research investigations in "model systems" that are simpler to work with in a precisely defined and controlled setting.

In the simplest experimental setting, researchers often remove the context of the organism and cell altogether and study individual molecules. By isolating a single type of protein, for instance, scientists can study its physical properties, functional activity, and three-dimensional structure. Understanding the structure and function of a protein allows researchers to design molecules that can selectively turn it "off" or "on" and forms the basis for the development of many pharmaceutical agents. In addition, these types of studies allow researchers to uncover how particular mutations alter molecular structure and function to cause disease.

An understanding of how molecules behave in isolation, however, must always be connected back to how they behave in a cellular setting. Scientists can study the function and interaction of molecules in cells grown in culture dishes in the laboratory. With the power of modern molecular biology, scientists can introduce virtually any gene of interest into a cell line to understand how it affects cellular outcomes, visualize how it interacts with different cellular components, and query how cellular processes are affected by particular disease-causing mutations. In addition to studying individual molecules in a cellular setting, researchers are more recently turning to "-omics" technologies to generate a systemwide picture of all of the molecules in a cell. This includes determining the sequences of all the genes in a certain cellular context (genomics), generating a profile of all the genes that are turned on or off in response to particular stimuli (transcriptomics), mapping out all of the protein-protein interactions and how they are modulated in different disease states (proteomics), following the path of all compounds generated by metabolism (metabolomics), and decoding the chemical markers that regulate gene expression (epigenomics). By amassing enormous data sets of gene sequences, protein-protein interactions, and gene expression profiles, systems biology researchers work to develop computational models to describe how all of these molecular components are integrated in normal health and disease.

Molecular Biology and Basic Research

With the power of modern molecular biology, scientists can introduce virtually any gene of interest into a cell line to understand how it affects cellular outcomes, visualize how it interacts with different cellular components, and query how cellular processes are affected by particular disease-causing mutations.

Finally, to provide the context of an organism, researchers will study biological processes in model organisms, including bacteria, yeast, plants, worms, fruit flies, fish, rodents, non-human primates, and many other organisms. Because human cells contain essentially the same molecular building blocks and pathways as these other organisms, model organisms can serve as powerful surrogates in the quest for understanding human biology and behavior. For example, certain biological processes, such as DNA replication, have been studied in detail in the single-celled organisms such as bacteria and yeast. In addition, the ability to manipulate particular genes of interest in relatively short developmental periods make worms and fruit flies powerful systems for studying normal and impaired developmental processes. Finally, as a mammalian relative, mice have served as an important system for generating animal models of human diseases and behavior. Researchers can introduce or alternatively "knock out" particular genes or cells to generate a physiological, behavioral, or disease "phenotype" of interest and examine the molecular basis for disease onset, progression, and treatment.

Advances in Basic Research Form the Building Blocks for Clinical Discovery and Improvements in Public Health

Progress in basic research does not necessarily follow a linear path from test tubes to cell culture to animal models as outlined above. Instead, basic research advances result from a continuum of collaborative interactions between research groups across multiple disciplines. The discovery of a gene that causes a diseased state in mice may spark the creation of research programs aimed at understanding the structural basis for how that gene's protein product interacts with a partner molecule as well as cellular studies to elucidate a novel molecular pathway that they regulate to generate a biological response. Conversely, the visualization of a previously unknown protein structure may provide remarkable insight on the protein's function and generate a hypothesis for how a particular mutation may generate a relevant disease model in mice. Regardless of the path taken to arrive at an incremental advance or a groundbreaking discovery, basic research lays the foundation for clinical advances that improve public health. At the heart of every clinical discovery is a body of fundamental basic knowledge that provides the impetus for setting forth a clinical hypothesis and generating the information required to safely and ethically proceed to testing in humans.

As an example of how advances in basic research build the foundation for clinical discovery and improvements in public health, NIH-supported investigators have recently discovered a novel approach for targeting the infectious bacterium *Staphylococcus aureus*; this is an important public health concern given the increasing resistance of *S. aureus* to conventional antibiotics. In 2005, a team of researchers discovered that the pigment molecule that gives *S. aureus* its golden color also serves to protect the bacteria from being killed by the human immune system following an infection.³¹ Having seen this result, another NIH-funded scientist, who studies how the human body makes cholesterol, observed that the protein and molecular machinery used to make the bacterial pigment molecule is very similar to that used to make cholesterol in humans; in fact, the first steps are nearly identical.³² Based on this observation, the two research teams, working together, went on in 2008 to demonstrate that cholesterol-lowering drugs that target a protein in humans also can be used to block *S. aureus* pigment synthesis.³³ Moreover, when these drugs are administered to mice infected with *S. aureus*, the mice are better able to kill the bacteria and overcome the infection than mice that did not receive the drug. With basic, fundamental knowledge of the proteins and pathway used to make this bacterial "virulence factor," this group of scientists has gone on to design new molecules that are more effective at blocking pigment production and reducing *S. aureus* virulence.³⁴ Having shown promising results in animal models, the years of collective, and initially unconnected, basic research that led to the development of this novel antimicrobial approach may offer a new strategy for reducing the public health burden of antibiotic-resistant *S. aureus* infection in humans.

Summary of NIH Activities

NIH supports a comprehensive portfolio of molecular biology and basic research aimed at understanding fundamental life processes. The results of such studies provide insights on fundamental aspects of biology and lay the foundation for other studies that will lead to ways to extend healthy life and reduce the burdens of illness and disability. In fact, each new finding serves as a building block for establishing a deeper understanding of human health and disease.

NIH supports general basic research, as well as basic research focused within a specific area or context. For example, NIH supports studies aimed at understanding the immune system in general, such as a program to better define human immune responses to infection or vaccination,³⁵ and also studies focused on understanding a particular aspect of the immune system, such as the immune response to specific pathogens (e.g., HIV, influenza virus, *Mycobacterium tuberculosis*) and immune-mediated diseases (e.g., allergies, type 1 diabetes, lupus, rheumatoid arthritis, primary immunodeficiency disorders).

Model Organisms and Systems

Basic research using model systems and organisms has provided the foundation of knowledge on which much of what is known about human growth and development, behavior, and the maintenance of wellness and development of disease has been learned. Research on bacteria, yeast, insects, worms, fish, rodents, primates, and even plants has shown that the basic operating principles are nearly the same in all living organisms; therefore, a finding made in fruit flies or mice may shed light on a biological process in humans. The fundamental knowledge created through studies of model systems and organisms has led to new methods for maintaining health and diagnosing and treating disease. (Also see the section on *Technology Development* in Chapter 3).

When scientists discover that a particular gene is associated with a disease in humans, one of the first things they typically do is find out what that gene does in a model organism. This often provides important clues for understanding the cause of a disease and for developing potential treatments. NIH supports the development and distribution of collections of animal systems with defects in known genes. These can be used to investigate how a particular gene found to be associated with a particular disease affects development overall and disease susceptibility and progression. For example, the NIH-sponsored National Resource for Zebrafish, *Drosophila Stock Center*, and *Caenorhabditis Genetics Center* provide the research community with well-characterized wild-type (normal) and mutant zebrafish, fruit flies, and roundworms, respectively.

NIH supports the development and distribution of collections of animal systems with defects in known genes. These can be used to investigate how a gene that is associated with a particular disease affects disease susceptibility and progression.

Model organisms often are especially useful for clarifying medical problems that have similar molecular causes. For example, protein clumping defects are common to several neurological disorders such as Alzheimer's, Parkinson's, and Huntington's diseases. Scientists can recreate these cellular defects in yeast, worms, and fruit flies, and then the findings can be translated into knowledge to benefit people with those diseases.

In addition to supporting studies of model organisms, NIH supports the development of a wide range of research models, particularly marine invertebrates and lower vertebrates, and the identification and development of new and improved animal models for the study of human diseases. For example, in 2008, NIH-funded researchers reported the development of a new mouse model for food allergy that mimics symptoms generated during a human allergic reaction to peanuts.³⁶ The animal model provides a new research tool that will be invaluable in furthering the understanding of the causes of peanut and other food allergies and in finding new ways to treat and prevent their occurrence.

Molecular Biology and Basic Research

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Molecular Mechanisms, Pathways, and Networks

In the human body, all biological components—from individual genes to entire organs—work together to promote normal development and sustain health. This amazing feat of biological teamwork is made possible by an array of intricate and interconnected pathways that facilitate communication among genes, molecules, and cells. While some of these biological pathways already have been discovered, many more remain to be found. Further research also is needed to understand how these pathways are integrated in humans and other complex organisms, as well as to determine how disturbances in these pathways may lead to disease and what might be done to restore disturbed pathways to their normal functions.

NIH supports a broad spectrum of research aimed at improving the molecular-level understanding of fundamental biological processes and discovering approaches to their control. In 2008, for example, NIH-supported researchers discovered that the activation of a novel set of proteins plays an important role in the development and persistence of chronic neuropathic pain conditions.³⁷ This discovery points scientists toward new targets for possible interventions that block the development of chronic pain. In another advance supported by NIH during FYs 2008 and 2009, scientists discovered two molecules that are important for tumor formation in head and neck cancers.³⁸ By uncovering how these molecules function in a key signaling pathway, scientists may be able to develop therapies that target them for the treatment of these devastating cancers. As in these studies, the goals of research supported by NIH in this area include an improved understanding of drug action; pharmacogenetics and mechanisms underlying individual responses to drugs; new methods and targets for drug discovery; advances in natural products synthesis; an enhanced understanding of biological catalysis; a greater knowledge of metabolic regulation and fundamental physiological processes; and the integration and application of basic physiological, pharmacological, and biochemical research to clinical issues.

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Cell and Molecular Biology

Growth and development is a life-long process that has many phases and functions. Much of the research in this area focuses on cellular, molecular, and developmental biology to build understanding of the mechanisms and interactions that guide a single fertilized egg through its development into a multicellular, highly organized adult organism. The eventual goal of these studies is to improve the diagnosis, treatment, cure, and prevention of human genetic and developmental disorders and diseases. (Also see the sections on *Life Stage, Human Development, and Rehabilitation* in Chapter 2 and *Genomics* in Chapter 3).

Just like a living creature, an individual cell has life stages. It is "born" (usually when its parent cell divides in two); it carries out its biological functions; it reproduces by dividing, often dozens of times; and it dies. Underlying these milestones are regular cycles, which can last from less than an hour to years or even decades. Progress through each cycle is governed by a precisely choreographed biochemical cascade involving a repertoire of molecules.

For the past several decades, NIH-supported researchers have conducted detailed studies of molecules that guide cells through division and development, methodically unraveling their biochemical identities and properties. The scientists have examined the molecules' ebb and flow throughout the cell cycle and their eventual demise as they are chemically chewed up when their job is done—until generated again for the next cell cycle. As for most life processes, when the biochemical choreography goes awry, the result can be disastrous.

Glitches in the cell cycle can lead to a host of diseases, most notably cancer, which can be defined simply as uncontrolled cell division and the failure of programmed cell death. Scientists are poised to take advantage of the wealth of basic research on the cell cycle. They are testing scores of potential anticancer drugs that aim to bolster or block cell cycle molecules. For instance, researchers also are harnessing their knowledge of the cyclical fluctuations in cell cycle molecules to predict the aggressiveness of a cancer and to tailor treatments.

Stem Cells

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell.

Given their unique regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes, heart disease, Parkinson's disease, and Alzheimer's disease. Today, donated organs and tissues often are used to replace ailing or destroyed tissue, but the need for transplantable tissues and organs far outweighs the available supply. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases. However, much work remains to be done in the laboratory and the clinic to understand how to use these cells for cell-based therapies to treat disease.

One particularly interesting research project on regenerative medicine involves a collaboration between NIH intramural researchers and scientists at Walter Reed Army Medical Center. Working together, in 2008, these scientists discovered that tissue removed from traumatic wounds, either to promote healing of orthopedic injuries or to treat war-related injuries, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells.³⁹ Those cells could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest stem cells from other sources.

During FYs 2008 and 2009, NIH funded multiple research projects on the basic biology of human embryonic stem cells (hESC) and has developed initiatives to support fundamental research on a new kind of stem cell, called an induced pluripotent stem cell (iPS). iPS cells are reprogrammed from adult cells to a pluripotent state remarkably like hESC. These reprogrammed cells offer a powerful approach to generating patient-specific stem cells that ultimately may be used in the clinic. (Also see the section on *Ensuring Responsible Research* in Chapter 1 for a summary of NIH activities concerning guidelines for the use of embryonic stem cells).

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Basic Immunobiology and Inflammation

The human immune system is composed of a network of specialized cells that act together to defend the body against infection by organisms such as bacteria, viruses, and parasites, and also act to prevent cancer. Unfortunately, poorly regulated immune responses can result in the development of immune-mediated diseases that include asthma, allergy, and autoimmune syndromes such as rheumatoid arthritis, multiple sclerosis, type 1 diabetes, and inflammatory bowel disease. Furthermore, it is the immune system that is responsible for the rejection of transplanted organs and tissues, which imposes the need for strong drugs to prevent rejection in transplant patients. The lack of an immune response also can be very deleterious, thus increasing susceptibility to infection. Immunodeficiency disorders can be caused by inherited flaws in the immune system, as is the case with primary immunodeficiency diseases, and by pathogens such as HIV that destroy immune cells.

Molecular Biology and Basic Research

Although a great deal has been learned about how the immune system operates in both health and disease, there is still more to be learned that will lead to improved and novel methods to prevent or treat human disease. Thus, NIH supports basic science studies in immunobiology (the biology of the immune system) to provide a pipeline of potential new treatments and vaccines. Research in basic immunobiology focuses on the structural and functional properties of cells of the immune system and the proteins they secrete, the interactions of immune components with other physiological systems, and the processes by which appropriate immunoregulation (regulation of the immune system) is achieved to protect the body while still preventing immune attack on self tissues.

Inflammation is triggered by molecules secreted by immune cells. Acute inflammation is triggered by damage to tissue or cells, typically by pathogens or injury. Chronic inflammation has been implicated in the etiology of multiple diseases, including asthma, atherosclerosis, cancer, cardiovascular disorders, and neurodegenerative diseases. Although significant breakthroughs have occurred in our understanding of inflammation, research is needed to further understand inflammatory processes. NIH is funding research to uncover as-yet-unknown immune mechanisms and mediators of inflammation as well as genetic factors, environmental triggers, and the relationship of inflammation to disease.

One of NIH's newer activities in this arena is the Center for Human Immunology, Autoimmunity, and Inflammation (CHI), a trans-NIH intramural initiative launched in 2008 to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiology, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease.

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"-Omics" Approaches

Technological advances have fundamentally changed the conduct of molecular biology, making it possible to rapidly obtain information on the entire complement of biomolecules within a cell or tissue. For example, it is now possible to measure the expression of all genes (transcriptome) in a cell or tissue in less than a day, something that would have taken months if not years, just a decade ago. These advances have led to the accumulation of large datasets that scientists sift through using statistical methods, or bioinformatics, to understand how networks of cellular components work in concert to produce a state of normal health and to identify the key players that go awry as a cause or result of disease. For example, scientists may now examine the entire genome of an organism to identify genes associated with a particular trait (e.g., susceptibility to disease, developmental stage, physical trait such as height) or to compare the proteome (i.e., the entire complement of proteins) of a specific cell type with those of another (e.g., Alzheimer's brain cells vs. normal brain cells). This type of research is sometimes referred to as "hypothesis limited" because investigators cast a technological net to obtain information on the entire catalog of biomolecules within a cell or tissue before they set out to prove or disprove a specific hypothesis. (Also see the sections on *Genomics; Disease Registries, Databases, and Biomedical Information Systems; and Technology Development* in Chapter 3).

NIH has made a significant investment in genomics, transcriptomics, proteomics, and other types of "-omics" that seek to catalog a specific class or type of biomolecule, as well as bioinformatics and computational biology. This investment has led to an explosive growth in biological information, a rich resource that can be mined for clues about fundamental life processes, susceptibility to disease, and disease outcomes. This deluge of genomic information has, in turn, led to an absolute requirement for computerized databases to store, organize, and index the data and for specialized tools to view and analyze the data. NIH's National Center for Biotechnology Information (NCBI) is charged with creating automated systems for storing and analyzing knowledge about molecular biology, biochemistry, and genetics; facilitating the use of such databases and software by the research and medical community; coordinating efforts to gather biotechnology

information both nationally and internationally; and performing research into advanced methods of computer-based information processing for analyzing the structure and function of biologically important molecules. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.) The following projects provide a rich array of examples of "-omics" research supported by NIH.

The Blueprint of Life: Genomics

As exemplified by the Human Genome Project, the field of genomics aims to understand how the entire genome, or genetic composition, of a cell or an organism contributes to define development, physiology, and disease. With a map of the human genome in hand, NIH continues to support research to understand how variations in the genetic sequence among individuals contribute to health and disease. Research in the area of pharmacogenomics seeks to understand the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a beneficial response to a drug, a poor or adverse response to a drug, or no response at all. (Also see the section on *Genomics* in Chapter 3).

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Genes Don't Count for Everything: Epigenetics

While the genetic composition of an organism undoubtedly is an important determinant of health and disease, additional mechanisms are involved in interpreting the genome and guiding molecular, cellular, and developmental processes. In the emerging field of epigenetics, scientists are uncovering a complex code of chemical markers that influence whether genes are active or silent, independent of DNA sequence. While epigenetics refers to the study of a single gene or sets of genes, epigenomics refers to more global analyses of epigenetic changes across the entire genome. Epigenetic processes control normal growth and development and this process is disrupted in diseases such as cancer. Diet and exposure to environmental chemicals throughout all stages of human development, among other factors, can cause epigenetic changes that may turn certain genes on or off; research in animal models has revealed that particular parenting behaviors trigger epigenetic changes and alterations in physiological and behavioral function of offspring. Changes in genes that would normally protect against a disease, as a result, could make people more susceptible to developing that disease later in life. Researchers also believe some epigenetic changes can be passed on from generation to generation. NIH-funded scientists have demonstrated that epigenetic changes are associated with the development and growth of many types of tumors and several mental illnesses. In fact, epigenetic marks on a specific gene, the ribosomal RNA gene, have been associated with suicidal behavior. Moreover, in August 2008, NIH scientists uncovered the importance of a mammalian protein called Vezf1 in maintaining genomic integrity by regulating specific epigenetic marks on DNA at widespread sites in the genome.⁴⁰

The NIH Roadmap Epigenomics Program, which in FYs 2008 and 2009 funded more than 2 dozen projects and consortia under a series of initiatives, aims to stimulate research on understanding the role of epigenetic regulation of gene expression in the origins of health and susceptibility to disease. It is anticipated that this program will transform biomedical research by developing comprehensive reference epigenome maps, identifying novel epigenetic marks, and developing new technologies for comprehensive epigenomic analyses. Ongoing epigenomic projects include studies on cognitive decline, atherosclerosis, and Bisperol A exposure.⁴¹

We Are Not Alone: The Microbiome

In addition to understanding how human genes contribute to health and disease, NIH also is interested in understanding how bacteria affect human health. The body of a healthy human adult provides a home for an enormous bacterial ecosystem, with bacterial cells outnumbering human cells by a factor of 10 to 1. Despite misconceptions that often

Molecular Biology and Basic Research

associate all bacteria with disease, most of the natural bacterial flora is composed of commensal—or beneficial—species that actually provide necessary cellular functions (such as the digestion of certain nutrients in the intestines). Through the NIH Roadmap, the Human Microbiome Project aims to discover the composition of microbial communities that exist in different parts of the human body and understand how these communities are associated with human health and disease. (Also see the section on *Genomics* in Chapter 3.)

The Human Microbiome Project aims to discover the composition of microbial communities that exist in different parts of the human body and understand how these communities are associated with human health and disease.

Translating the Genetic Code: Transcriptomics, Proteomics, and Metabolomics

Beyond understanding genes and their regulation, NIH also supports systemwide studies to understand what genes are actually turned on and off and when (transcriptomics). Since genes code for the proteins that carry out almost all cellular functions, understanding which genes are active and, by extension, the catalog of proteins carrying out cellular functions (proteomics) in a given cell type under particular sets of conditions, provides a picture of the molecular players involved in normal and disease states. In one example, NIH supported a comprehensive analysis of the salivary proteome—a catalog of all the proteins present in saliva. This initial description of the salivary proteome, published in 2008, provides a significant first step toward a comprehensive understanding of saliva function and provides a source of potential diagnostic and prognostic biomarkers for oral and systemic conditions.⁴² In the growing field of metabolomics, researchers are using high-throughput methodologies to characterize the types and amounts of metabolic compounds present in our cells and to map the metabolic pathways and networks through which they are generated and regulated. By studying the network of chemical pathways and their chemical products, these types of studies have the capability of defining normal homeostatic and disease mechanisms. In February 2009, NIH-supported investigators reported using metabolomics to identify metabolic compounds associated with the progression from benign prostate tissue to prostate cancer.⁴³ Having identified pathways and compounds associated with disease progression, researchers can then use hypothesis-driven basic research experiments to further understand how particular proteins and molecules function in these pathways.

In February 2009, NIH-supported investigators reported using metabolomics to identify metabolic compounds associated with the progression from benign prostate tissue to prostate cancer.

Shape Matters: Structural Biology of Proteins

In addition to understanding the collective composition of proteins in a cell, researchers also aim to characterize their three-dimensional structures. The Structural Biology Roadmap is a strategic effort to create a "picture" gallery of the molecular shapes of proteins in the body. Of particular interest, NIH is focusing efforts on determining structures of the proteins that reside in the membrane barrier that separates the inside of the cell from the outside. These membrane proteins account for about 30 percent of the proteins in the cell and are major targets for developing therapeutic drugs to treat a particular disease by blocking, inhibiting, or activating the specific molecule. In a noteworthy example of structural advances made during FYs 2008 and 2009, NIH-supported scientists determined the three-dimensional structure of the β_2 -adrenergic receptor,^{44, 45} an important target of pharmaceutical agents; knowledge of this structure adds to our fundamental understanding of how this class of proteins functions and provides insight on how to design new and improved drugs.

The Sugar Coating: Glycomics

NIH is also interested in mapping out additional molecular compounds associated with cellular function. In one field, NIH is seeking to understand the role of glycans—complex chains of sugar molecules—in various cellular functions. Glycans often are found attached to the surface of cells and to proteins found on the cell surface, and they serve important roles in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. To advance the field of

"glycomics," NIH supports programs that develop technologies for the analysis of glycans in complex biological systems and has established the Consortium for Functional Glycomics, which provides access to a technological infrastructure for glycobiology in support of basic research. Recent findings indicate that basic research on glycosylation may lead to the development of a broad spectrum antiviral. Over several years, NIH researchers discovered three antiviral proteins that bind to sugar groups commonly found on the surfaces of many viruses, which prevent the viruses from entering cells and reproducing. In 2009, investigators reported that one particularly potent antiviral protein, known as griffithsin (GRFT), appears to work well against SARS and Ebola viruses, as well as HIV.⁴⁶ So far, GRFT has only been tested in animals and cell cultures, but results are promising.

Putting It All Together with Systems Biology

With the increasing application of "-omics" and high-throughput technologies, scientists are generating massive amounts of data on the genetic and molecular basis of biological processes and responses. In an effort to put all of this information together across multiple scales, NIH researchers are turning to and pioneering the emerging field of systems biology. Systems biology draws on the expertise of biology, mathematics, engineering, and the physical sciences to integrate experimental data with computational approaches that generate models to describe complex biological systems. In addition to describing the interactions among genes, proteins, and metabolites, the models are intended to be predictive of physiological behavior in response to natural and artificial perturbations. By monitoring the effects of a perturbation in "virtual" experiments, scientists can generate hypotheses to test in cellular systems or model organisms and gain a better understanding of the molecular contributions to normal health and disease.

To support initiatives in this area, NIH has established National Centers for Systems Biology. At 10 interdisciplinary centers, NIH-funded scientists are using computational modeling and analysis to study the complex dynamics of molecular signaling and regulatory networks involved in cell proliferation, differentiation, and death; developmental pattern formation in organisms; genome organization and evolution; and drug effects on cells, organs, and tissues. The Program in Systems Immunology and Infectious Disease Modeling, a component of NIH's intramural research program, seeks to apply a systems biology approach to characterize a complex biological system—the human immune system. In this effort, researchers are seeking to develop models that enhance our understanding of the molecular basis for an immune response to infection or vaccination. In another area of systems biology research, NIH supported the construction of a "metabolic network map" for the bacterium that causes severe, chronic periodontal disease.⁴⁷ This model describes the metabolic properties of the bacterium and can be used to predict the effect of the loss of certain genes or metabolic pathways on bacterial growth rate. As the first model of this type for an oral pathogen, this metabolic network map provides opportunities to discover new antibacterial drug targets. Finally, the NIH Integrative Cancer Biology Program (ICBP) is providing new insights into the development and progression of cancer as a complex biological system. Researchers at ICBP Centers are generating and validating computational models that describe and simulate the complex process of cancer, which should ultimately lead to better cancer prevention, diagnostics, and therapeutics.

The Program in Systems Immunology and Infectious Disease Modeling in NIH's intramural research program seeks to apply a systems biology approach to characterize a complex biological system—the human immune system.

Environmental Factors that Impinge on Human Health and Disease

Just as cells respond to changes in their microscopic environment, they also are responsible for sensing and responding to environmental factors present in our "macroscopic" human world. As part of its effort to reduce the burden of human illness and disability, NIH supports basic research efforts to understand how environmental factors are detected by our bodies and how, at the molecular and cellular levels, they influence the development and progression of human diseases. The National Toxicology Program (NTP), for example, is developing innovative methods to determine which of the many chemicals that humans are exposed to are toxic, with an aim of understanding how they impart their toxic effects on human cells. In another area, researchers at the Breast Cancer and the Environment Research Centers are using genomics

Molecular Biology and Basic Research

and proteomics approaches to study the impact of chemicals in the environment on mammary gland development and are evaluating how environmental exposures affect important cell-cell interactions. NIH also has established research programs to investigate the relationship between exposure to heavy metals, such as mercury, in the environment and the progression and development of autoimmune disorders; understanding at the molecular level how these agents impart immune system dysfunction could offer potential therapeutic targets for treating these disorders.

Role of Basic Behavioral and Social Science Research

Recognizing the importance of behavioral and social factors in health and disease, NIH supports a broad portfolio of research in the basic behavioral and social sciences. Research in these areas provides fundamental knowledge and approaches that are essential for understanding individual and collective systems of behavior and psychosocial functioning; for predicting, preventing, and controlling illness; for developing more personalized (tailored) interventions; for enhancing adherence to treatment and minimizing the collateral impact of disease; and for promoting optimal health and well-being across the lifespan and over generations. Priority areas in basic behavioral and social sciences research include: gene-environment interactions; systems models and procedures for measurement, analysis, and classification; intergenerational transmission of behavior; biopsychosocial stress markers; and social integration and social capital.

At NIH, the mission of supporting basic behavioral and social science research is shared across ICs and OD Offices. To pursue shared opportunities and address common interests, NIH created the trans-NIH initiative known as the NIH Basic Behavioral and Social Science Opportunity Network (OppNet) in 2009. The purpose of OppNet is to pursue opportunities for strengthening basic behavioral and social sciences research while expanding and innovating beyond existing investments in these areas.

Basic behavioral and social sciences research supported by NIH is comprised of research on behavioral and social processes, biopsychosocial research, and research on methodology and measurement. Within the first category is research on behavior change, including the study of factors that shape health decision-making (e.g., cognitive, social, environmental, and developmental) and the conditions under which knowledge leads to action vs. inaction. Basic behavioral economic and decision research approaches—such as "choice architecture," which describes the way in which decisions are influenced by how the choices are presented, as well as the use of financial incentives to promote behavior change—are yielding findings that may be translated into effective interventions to change behavior and improve health. Basic research on social networks is improving our understanding of how smoking and obesity spread through socially connected individuals and provides insight into how networks might be used as vehicles to spread healthy behaviors.

Biopsychosocial research includes research on gene-environment interactions and other biobehavioral processes. The Exposure Biology Program of the NIH *Genes, Environment and Health Initiative* supports the development of tools to measure dietary intake, physical activity, psychosocial stress, and addictive substances—aspects of the behavioral and social environment—in addition to tools to measure environmental pollutants, for future use in studies of gene-environment interactions. Biopsychosocial research in humans and rodent models is elucidating how psychosocial stressors influence biological pathways involved in the growth and spread of cancer. Knowledge gained from biopsychosocial research will inform interventions to prevent, manage, and treat a variety of diseases and disorders.

The Exposure Biology Program of the NIH Genes, Environment and Health Initiative supports the development of tools to measure dietary intake, physical activity, psychosocial stress, and addictive substances—aspects of the behavioral and social environment—in addition to tools to measure environmental pollutants, for future use in studies of gene-environment interactions.

Methodological development in the behavioral and social sciences includes a new emphasis on systems science approaches. Much like the systems approaches to biology described above, systems science examines the multilevel, complex interrelationships among the many determinants of health—biological, behavioral, and social—to provide a way

to address complex problems within the framework of the "big picture." Systems science involves developing computational models to examine the dynamic interrelationships of variables at multiple levels of analysis (e.g., from cells to society) simultaneously (often through causal feedback processes), while also studying impact on the behavior of the system as a whole over time. For instance, systems science methodologies are beginning to be employed for planning and preparing against acute threats to public health such as global spread of a pandemic influenza. The Models of Infectious Disease Agent Study (MIDAS) is a collaboration of seven multi-institutional research and informatics groups focused on developing computational models of the interactions between infectious agents and their hosts, disease spread, prediction systems, and response strategies. The models will be useful to policymakers, public health workers, and other researchers who want to better understand and respond to emerging infectious diseases. Chronic diseases and risk factors for which systems science approaches would enhance our understanding and decision-making capacity include heart disease, diabetes, obesity, high blood pressure, eating behavior, physical activity, smoking, and drug and alcohol use.

Research Resources, Infrastructure, and Technology Development

In building the foundation for its broad portfolio of basic research programs, NIH also makes significant investments in the development of research resources, infrastructure, and state-of-the-art technologies that facilitate the next discoveries in biomedical and behavioral research. In line with its interest to ensure that research resources developed with NIH funding are made readily available to the research community for further research, NIH supports multiple repositories for the collection and dissemination of animal models, cell lines, and other vital biomedical research reagents. Repositories are updated continuously as resources become available and include the Mutant Mouse Regional Resource Centers, which stores, maintains, and distributes selected lines of genetically engineered mice; the National Stem Cell Bank, which makes human embryonic stem cell lines readily available; and the Beta Cell Biology Consortium, which generates animal models and antibodies that are available to the scientific community for research on type 1 and type 2 diabetes.

In addition to animal models and research reagents, NIH also supports the distribution of massive amounts of genome sequence, transcriptional profiling, and cellular structure function data for use and analysis by the research community at large. NIH continues to serve as a leading global resource for building, curating, and providing sophisticated access to molecular biology and genomic information. This includes databases such as Genbank, a collection of nearly all known DNA sequences that also provides access to the assembled Human Genome Project data. In addition to databases, NIH also provides resources for retrieving, visualizing, and analyzing molecular biology and genome sequence data online. Other examples of data sharing resources include the Biomedical Informatics Research Network, which supports the integration of data, expertise, and unique technologies to advance research on Alzheimer's disease, autism, and other areas of neuroscience; and the Influenza Virus Resource, which provides a database of influenza virus genome sequences that may help researchers identify potential therapeutic, diagnostic, and vaccine targets. Together, it is expected that the timely sharing of research resources and data housed in these and other databases will further the research enterprise for the betterment of public health. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3).

NIH continues to support the Shared Instrumentation and High End Instrumentation Grant Programs to ensure that NIH-supported investigators have access to state-of-the-art technologies necessary to fulfill their research goals.

NIH continues to support the development and maintenance of our Nation's research infrastructure. Since many areas of biomedical research require the use of sophisticated instrumentation, NIH continues to support the Shared Instrumentation and High End Instrumentation Grant Programs to ensure that NIH-supported investigators have access to state-of-the-art technologies necessary to fulfill their research goals. Critical to this infrastructure is support for biocontainment laboratories that allow scientists to study highly contagious, life-threatening pathogens in a safe and secure setting. NIH also continuously seeks to improve the current "state-of-the-art" in different technology areas. This is highlighted by the NIH-supported Biomedical Technology Research Centers that develop innovative technologies to aid researchers who are studying virtually every human disease. (Also see the section on *Technology Development* in Chapter 3.)

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research

I = Supported through **I**ntramural research

O = **O**ther (e.g., policy, planning, or communication)

COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program

GPRG Goal = **G**overnment **P**erformance and **R**esults **A**ct

ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Model Organisms and Systems

Zebrafish Help Scientists Identify Susceptibility Genes for Hearing and Balance Loss, and Drugs that May Prevent

It: The sensory hair cells in the inner ear are topped with tiny, hair-like projections that detect sound or head position and movement (important for maintaining balance). Individuals demonstrate varying susceptibility to hair cell damage, which can be due to exposure to certain antibiotics, chemotherapy, other chemical agents; prolonged exposure to loud sounds; and in aging. Hair cell damage leads to hearing and balance disorders. Scientists working to understand the reason for this variability in susceptibility have used the zebrafish lateral line to model human hair cell damage. The lateral line on the fish's side contains sensory cells that detect the fish's position and motion in water. Hair cells in the lateral line function similarly to the hair cells in the human inner ear, and NIH-supported scientists exploited this to develop an important screening system. After generating fish with random mutations, the scientists subjected the mutant fish's exposed sensory cells to a potentially damaging antibiotic drug. By identifying the specific genetic mutations present in the fish and noting how the lateral line was affected by the antibiotic insult, the scientists are beginning to understand which genetic variations may be important for hearing and balance damage susceptibility. They also used the zebrafish model to study the effects of antibiotic insult combined with treatment using potentially protective substances to identify substances that seem to protect the sensory cells from damage—thus preventing potential hearing and balance disorders. The insight gained may help scientists develop personalized treatments based upon an individual's genetic makeup, and may enable prevention of some hearing and balance disorders via careful administration of protective drugs. These approaches increasingly will become important as the Nation's health care system faces the challenge of treating the aging Baby Boomer generation, many of whom already have hearing and balance problems.

→ Owens KN, et al. *PLoS Genet* 2008;4(2):e1000020. PMID: 18454195. PMCID: PMC2265478.

→ (E) (**NIDCD**)

Researchers Discover Why Mammalian Teeth Form in a Single Row: Why do mammals develop a single row of teeth whereas other vertebrates, such as sharks, can develop multiple rows of teeth? Researchers studying mutations in the genes of mice that develop teeth serving no apparent function may have solved the mystery. Most of the mutations under study caused the mice to develop the extra teeth within the space between the normal incisor and the normal first molar. Since tooth buds normally develop within this part of the developmental field but later regress, these genetic alterations did not alter the normal plane within which teeth developed. However, one particular mutation had a different result. The researchers found that a knockout mutation (i.e., elimination) of a gene known as Odd-skipped related 2 (*Osr2*) also resulted in the production of extra teeth, but strikingly, these teeth developed outside the usual plane, on the tongue side of the normal molars, suggesting that the mutation results in an expansion of this developmental field in the affected mice. Supporting this theory, the knockout mice (i.e., mice lacking *Osr2*) have spatially expanded expression of other genes

involved in tooth development. That suggests that normal *Osr2* acts to restrict tooth development to within its usual, single-row plane. Previous work from this group discovered the *Osr2* gene and demonstrated that it is a novel regulator of palate formation. The current study demonstrates that *Osr2* function also is critical to the patterning of tooth formation and sheds light on the restriction of teeth to a single row in mammals. *Osr2* function may be an important consideration for researchers seeking to grow replacements eventually for lost teeth in adults.

- Zhang Z, et al. *Science* 2009;323:1232-4. PMID: 19251632. PMCID: PMC2650836.
- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/CurrentSNIB/March/SingleRow.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*
- (E) (NIDCR)

Molecular Mechanisms, Pathways and Networks

New Method to Synthesize Molecules: During the past year, NIH-supported researchers discovered a new method for the preparation of a small heterocyclic molecule containing three rings that was completely unprecedented in the literature. The discovery of a ready access to novel heterocyclic scaffolds is a key contribution to innovative pharmaceutical research. Seventy analogs of this new molecule were made, and biological studies revealed potent and selective activities at G-protein coupled receptors, a biological target that accounts currently for approximately 50 percent of all new drugs.

- Walczak MA, Wipf P. *J Am Chem Soc* 2008;130 (22):6924-5. PMID: 18461936. PMCID: PMC2754197.
- (E) (NIGMS) (GPRA)

Evolutionary Analysis of Protein Domains: A group of investigators at NIH employ the latest techniques in the field of computational biology to study fundamental biological problems such as molecular evolution. Elucidating the biochemical and biological functions of protein domains is central to understanding basic life processes. (A "protein domain" is a discrete section of a protein that has its own function and can evolve independently.) Computer simulations, based on evolutionary principles, are used for the discovery, classification, evolutionary analysis, and biochemical predictions of protein domains and domain architectures. An important dimension in this type of research is discovery of "new" domains that are shared by many diverse proteins but have not been defined previously. An example of this research is the prediction of the function of the *DBC1* gene, which is deleted in a prevalent form of breast cancer. Analysis of the complex domain architectures of the members of the *DBC1* family suggest that they are likely to function as integrators of distinct regulatory signals, and the findings also suggest the possibility for developing new therapeutics based on soluble small molecules.

- Anantharaman V, Aravind L. *Cell Cycle* 2008;7(10):1467-72. PMID: 18418069. PMCID: PMC2423810.
- (I) (NLM)

New Targets Identified for Intervention in the Development of Head and Neck Cancers: Over the last decade, cancer researchers have made significant progress in defining the molecular pathways involved in the development of head and neck squamous cell cancer. Studies that identify and characterize "key players" hold tremendous promise for the future treatment of these devastating cancers and ultimately improve the overall survival and quality-of-life for afflicted patients. One such key player is a family of proteins known as Wnt. Aberrant activation of the Wnt pathway has been found to be associated with cancer development and progression. Wnt promotes initiation of cancer by increasing the nuclear accumulation of β -catenin, an integral component of Wnt signaling, to activate target genes downstream. However, the mechanism of β -catenin recruitment to the Wnt target gene promoter largely is unknown. In an elegant study, the researchers discovered that β -catenin interacted with two other molecules (commonly called TBL1 and TBLR1), leading

Molecular Biology and Basic Research

to the recruitment of β -catenin to the promoter of Wnt target genes. Decreasing TBL1 or TBLR1 via genetic knock-down did not affect the nuclear accumulation of β -catenin, but it did inhibit β -catenin significantly from binding to Wnt target gene promoter and the expression of Wnt target genes associated with tumor development. Moreover, depletion of TBL1 or TBLR1 inhibited invasive growth of tumor cells. These results provide fundamental knowledge about tumor genesis by revealing two new components required for nuclear β -catenin function. Targeting these molecules can have important therapeutic implications for head and neck cancer.

- Li J, Wang C-Y. *Nat Cell Biol* 2008;10(2):160-9. PMID: 18193033.
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*
- (E) (NIDCR)

New Model Reveals Novel Molecular Strategies in the Fight to Overcome Oral Cancer: Oral and pharyngeal carcinomas are the ninth most common cancer worldwide, with more than 35,000 new patients and more than 7,500 deaths each year in the United States alone. The 5-year survival rate has improved only marginally over the past 40 years. There is an urgent need for new options for these patients. Emerging information on the deregulation of normal molecular mechanisms that result in the cancer's progression provides the possibility of new mechanisms-based therapeutic approaches for these aggressive oral malignancies. NIH scientists recently used a two-step chemical carcinogenesis model and found that the drug rapamycin exerted a remarkable anticancer activity. It decreased the tumor burden of mice having early and advanced tumors, and even brought about the regression of recurrent squamous cell skin cancers. The scientists reported that the persistent activation of mTOR, the mammalian Target of Rapamycin, occurs frequently in head and neck cancer patients and that its inhibition by rapamycin causes regression of human oral cancer tumors implanted in mice. Because chemically induced animal cancer models often better reflect the complexity of the clinical setting, the scientists developed an oral-specific chemical carcinogenesis mouse model. In this model, activation of mTOR is an early event in precancerous lesions; rapamycin treatment can halt the malignant conversion of precancerous lesions and promote the regression of advanced carcinogen-induced oral squamous cell carcinomas (SCCs). Significance: The development of this SCC carcinogenesis model demonstrates that the use of mTOR inhibitors may provide a novel molecular-targeted strategy for chemoprevention and treatment of oral squamous cell cancer.

- Amornphimoltham A, et al. *Clin Cancer Res* 2008;14(24):8094-101. PMID: 19073969.
- Czerninski R, et al. *Cancer Prevention Res* 2009;2(1):27-36. PMID: 19139015.
- For more information, see <http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/OralCancer/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*
- (I) (NIDCR)

Tumor Biology, Microenvironment, and Metastasis: The Tumor Biology and Metastasis Program supports research delineating the molecular mechanisms and signaling pathways involved in tumor progression, cell migration and invasion, angiogenesis (growth of blood vessels), lymphangiogenesis (formation of lymphatic vessels), and metastasis. Novel areas of research include the contributions of bone marrow-derived cells to tumor formation, progression, and metastasis; the role of dormant cells and their microenvironment; the role of host tissue microenvironment in organ-specific metastasis; characterization of the heterogeneity within the tumor microenvironment; and the characterization of cancer as a systemic disease. The Tumor Microenvironment Network (TMEN) investigates mechanisms of tumor-stroma interactions in human cancer. (Stroma is the connective tissue that supports or surrounds other tissues and organs.) In addition to delineating the role of host stroma in carcinogenesis, TMEN investigators are generating novel reagents that can be shared with the research community. The Cancer Immunology/Hematology Program supports research on the cellular and molecular characterization of tumor stem cells, which are minor populations of tumor cells that may be responsible for recapitulating all the cell types in a given tumor and causing metastasis due to their unique self-renewal properties. In FY 2008, NIH sponsored two RFAs on tumor stem cells aimed at enhancing synergistic research between basic scientists and translational scientists working on tumor stem cells. In addition, a program announcement for Stem Cells and Cancer was

released to stimulate efforts to isolate and characterize tumor stem cells from a large spectrum of tumors to understand better the progression of malignant disease.

- For more information, see <http://tmen.nci.nih.gov>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-019.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-020.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-165.html>
- This example also appears in Chapter 2: *Cancer*
- (E) (NCI)

Glucosamine and Chondroitin Fare No Better Than Placebo in Slowing Structural Damage of Knee

Osteoarthritis: Osteoarthritis affects an estimated 27 million Americans, and researchers are seeking ways not only to treat pain, but also to address the loss of cartilage—a hallmark of the condition. The two-part Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), funded by NIH, investigated whether this dietary supplement can treat pain and diminish structural damage associated with knee osteoarthritis. In the primary study (GAIT I), combined glucosamine/chondroitin sulfate did not provide significant relief among study participants overall, although a smaller subgroup with moderate to severe pain did show significant relief. The 18-month GAIT II ancillary study followed cartilage loss in GAIT participants with moderate or severe osteoarthritis in one or both knees, comparing the effects of glucosamine and/or chondroitin sulfate with placebo. In GAIT II, glucosamine and chondroitin—together or alone—appeared to fare no better than a placebo in slowing loss of cartilage in osteoarthritis of the knee, measured by joint space width as seen on x-rays. Interpreting the study results is complicated, however, because participants taking placebo had a smaller loss of cartilage than predicted. In addition to its findings on the effects of dietary supplements taken by many Americans for osteoarthritis, GAIT II provided new insights on osteoarthritis progression, techniques for measuring loss of joint space width, and characteristics of osteoarthritis patients who may respond best to glucosamine/chondroitin.

- Sawitzke AD, et al. *Arthritis Rheum* 2008;58(10):3183-91. PMID: 18821708.
- For more information, see <http://nccam.nih.gov/news/2008/092908.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NCCAM, NIAMS)

Promising Approaches to Treating Chronic Pain: Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can result in addiction, tolerance, and physical dependence, all of which may undercut their value in some patients. Thus, an area of enormous need is the development of potent analgesics with diminished abuse liability for treating chronic pain. In response, NIH has implemented an aggressive and multidisciplinary research program that is yielding tangible results, which stand to revolutionize the field of pain management. At the molecular level, cannabinoid (CB) research has shown that it is possible to activate the CB system selectively to provide analgesia with minimal or no effects on mental function, and no abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different (heteromeric) receptors. Targeting them could provide a vastly expanded range of pharmacotherapeutics. This approach has already ushered in the development of promising designer molecules that can block pain more selectively and safely. At the cellular level, active research on non-neuronal brain cells has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their proinflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of other analgesic drugs. At the brain circuit level, a new approach has been developed to harness the brain's intrinsic capacity to train itself through a strategy in which subjects "learn" how to regulate pain by viewing, and then controlling, images of their own brains in real time.

- Varga EV, et al. *Curr Mol Pharmacol* 2008;1(3):273-84. PMID: 20021440.
- Ferre S, et al. *Trends Neurosci* 2007;30(9):440-6. PMID: 17692396.

Molecular Biology and Basic Research

Daniels DJ, et al. *Proc Natl Acad Sci U S A* 2005;102(52):19208-13. PMID: 16365317. PMCID: PMC1323165.

Ledeboer A, et al. *Expert Opin Investig Drugs* 2007;16(7):935-50. PMID: 17594181.

deCharms RC. *Trends Cogn Sci* 2007;11(11):473-81. PMID: 17988931.

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDA, NINDS)

Peripheral Neuropathies: NIH funds studies focused on understanding the genetic basis and molecular and cellular mechanisms of many peripheral neuropathies, including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, inherited neuropathies such as Charcot-Marie-Tooth, inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy, and rare forms of peripheral neuropathy. Other notable projects include a natural history study of diabetic neuropathy, projects to improve the efficiency and effectiveness of diagnosis for various peripheral neuropathies, and a Phase III clinical trial to treat Familial Amyloidotic Polyneuropathy. In August 2008, a pair of program announcements was released to promote translational research in neuromuscular disease. Diseases included in these program announcements are those that affect the motor unit—the motoneuron, its process (axon), and the skeletal muscle fiber that is innervated by the neuron—such as peripheral neuropathy, amyotrophic lateral sclerosis, and muscular dystrophy. This unique structure-function framework provides a coordinated approach for therapeutic development in a subset of neurological diseases that share many common features, including the peripheral neuropathies.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E) (NINDS, NIDDK)

Understanding the Roles of Non-Neuronal Cells in Neuropathic Pain Provides New Targets for

Intervention: Chronic pain caused by nerve injury, called neuropathic pain, is difficult to treat because we do not yet fully understand the biological mechanisms underlying its development and persistence. Most pain-relieving medications for chronic pain target nerve cells, yet it is becoming clear that non-nerve (non-conducting) cells also play an important role in some chronic pain conditions. Matrix metalloproteases (MMPs) are enzymes that break down the medium surrounding tissue cells. MMPs also activate several pro-inflammatory proteins that stimulate the non-nerve conducting function of the supportive glial cell. Scientists are wondering if neuropathic pain and inflammation are linked by a common mechanism involving MMP activation. Researchers found that a specific matrix metalloprotease, MMP9, showed increased activity soon after nerve injury, which stimulated the glial cells in the spinal cord, but this increased activity declined after several days. A different enzyme, MMP2, also was increased, but at later times after injury; this increase led to activation of another nerve-supportive cell in the spinal cord. The research showed that the pain response of nerve-injured animals were blocked early by inhibitors of MMP9 or later by inhibitors of MMP2. These findings suggest an important role for MMP9 in the onset of chronic neuropathic pain conditions, and for MMP2 in the persistence of those conditions. The results also demonstrate the complex interplay between nerve cells and several non-nerve cells. This research describes a novel set of molecules involved in neuropathic pain, and points scientists toward new targets for possible interventions to short-circuit the onset and persistence of chronic pain conditions.

- Kawasaki Y, et al. *Nat Med* 2008;14(3):331-6. PMID: 18264108. PMCID: PMC2279180.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDCR)

From Genes to Therapy in Neurogenetic Disorders: Neurofibromatosis (NF) and tuberous sclerosis complex (TSC) are neurogenetic disorders that cause tumors on nerves, in the brain, and on other organs. Although the tumors are benign, consequences of their size and location can be serious. Clinical manifestations can include seizures, autism, and cognitive disability. NIH support led to identification of the genes underlying these disorders, and recently has enabled investigators to uncover disease mechanisms that point to strategies for therapeutic development. One NF study revealed that an NF1 gene mutation in bone marrow cells (which infiltrate peripheral nerves prior to NF tumor development) is necessary for tumor growth. Activation of c-kit, a molecule implicated in some cancers and targeted by the cancer drug Gleevec, enables release of the cells from bone marrow to stimulate neurofibroma growth. In this study, Gleevec treatment prevented formation and reduced neurofibroma size and activity. If clinical trials prove successful, Gleevec could become the first approved NF treatment. In TSC, genetic mutations cause deregulation of an anti-tumor molecule, mTOR, which is a known target of rapamycin (a drug currently used to treat organ transplant rejection). In previous studies, rapamycin reduced the size of brain and kidney tumors in TSC patients. Recent NIH-supported research in mice revealed that rapamycin, via the mTOR pathway, inhibited TSC-induced brain enlargement and mortality, prevented seizures, and improved cognitive ability in mice, results which have led to clinical trials now in Phase III. Rapamycin also alleviated seizures in a rat model of epilepsy, which may shed light on TSC-associated neurological diseases, including autism and epilepsy.

- Ehninger D, et al. *Nat Med* 2008;14(8):843-8. PMID: 18568033. PMCID: PMC2664098.
- Meikle L, et al. *J Neurosci* 2008;28(21):5422-32. PMID: 18495876. PMCID: PMC2633923.
- Yang FC, et al. *Cell* 2008;135(3):437-48. PMID: 18984156. PMCID: PMC2788814.
- Zeng LH, et al. *J Neurosci* 2009;29(21):6964-72. PMID: 19474323. PMCID: PMC2727061.
- Zeng LH, et al. *Ann Neurol* 2008;63(4): 444-53. PMID: 18389497.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NINDS, NCI, NICHD, NIMH)

Insights into the Molecular Interplay Governing Formation of Cranial Sensory Ganglia: The developmental biology underlying sensory nerve development is fascinatingly intriguing. Take the trigeminal ganglion, which is responsible for touch, pain, and temperature sensation for most of the face. How do precursor cells self-organize in the embryo to produce an anatomically correct sensory network connecting to the central nervous system? Many of the answers are wired into the molecular circuitry of two transient embryonic cell types called neural crest cells and ectodermal placodes. They interact during embryonic development to differentiate into the nerve cells that form the trigeminal ganglion. But virtually nothing is known about the molecular interplay that mediates this interaction. It is a biological puzzle with no known pieces. Now NIH grantees have introduced the first two pieces of the puzzle. They demonstrated in animal studies that the cranial subtype of neural crest cells express the protein Slit1 on their surface during their programmed migration to the trigeminal-forming ectodermal placodes. Meanwhile, as the trigeminal placode cells follow their developmental program, they express on their surface the Robo2 protein, which is the receptor for the Slit1 protein. The Robo2-Slit1 connection, like fitting a hand in a glove, mediates the interaction of neural crest and trigeminal placode cells during the formation of sensory ganglia. When the scientists disrupted one or both molecular signals, the resulting sensory ganglia were abnormal. The teams' findings are important to understanding the mechanisms that regulate formation of the sensory nervous system and thus provide potential targets for identifying the causes of congenital sensory disorders involving the neural crest cell population.

- Shiau CE, et al. *Nat Neurosci* 2008;11(3):269-76. PMID: 18278043.
- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/Archive/archive2008/April/TrigeminalGanglion.htm>
- For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18278043?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Molecular Biology and Basic Research

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDCR)

Neurobiology of Appetite Control: NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. For example, the sight of food has been found to induce different responses in the brains of patients following weight loss; these differences are due to changes in levels of the hormone leptin. Researchers also discovered that rats susceptible to becoming obese from a high-calorie diet have fewer neural connections in the brain in the hypothalamus (the part of the brain that has a key role in weight regulation) compared to normal rats. Additionally, a factor secreted by the small intestine in response to dietary fat intake has been found to enter the brain and suppress appetite in rats. More recently, six new genetic regions associated with obesity were identified and found to be in or near genes expressed in the brain. To highlight further the connection between brain function and obesity, a trans-NIH workshop on neuroimaging in obesity research was held to share data and experiences with functional neuroimaging approaches to study brain involvement in various aspects of obesity such as weight gain and loss, and the neurotransmitters and brain structures associated with energy balance, hunger, and decision-making. A recent funding opportunity announcement was issued to foster new research using neuroimaging approaches to enhance understanding of food intake and energy expenditure in the context of obesity. This research has implications for new therapies for obesity.

- Rosenbaum M, et al. *J Clin Invest* 2008;118(7):2583-91. PMID: 18568078. PMCID: PMC2430499.
- Bouret SG, et al. *Cell Metab* 2008;7:7(2):179-85. PMID: 18249177. PMCID: PMC2442478.
- Gillum MP, et al. *Cell* 2008;135(5):813-24. PMID: 19041747. PMCID: PMC2643061.
- Willer CJ, et al. *Nat Genet* 2009;41(1):25-34. PMID: 19079261. PMCID: PMC2695662.
- For more information, see <http://www3.niddk.nih.gov/fund/other/neuroimaging2008/>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/rfa-dk-08-009.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDDK)

Not Only In Your Mouth—Your Gut Can Taste, Too: Sugars consumed in food affect blood sugar levels differently than sugars given intravenously. Scientists have been examining sugar-binding molecules in the gut lining to determine why this happens. While the tongue has been known as the taste organ of the body, NIH-funded scientists recently have identified taste receptors in the human gut. Their data suggest that the human gut detects sugars in food through these taste receptors, and uses this information to turn up the production of blood sugar-regulation hormones, including the hormone that regulates insulin release. Individuals that have difficulty detecting and regulating sugar can gain weight more easily and/or develop other metabolic problems, including diabetes. The discovery of taste receptors in the lining of the gut may help scientists develop drugs that are specific to the gut taste receptors to treat weight problems and diabetes, two very significant public health issues.

- Jang HJ, et al. *Natl Acad Sci USA* 2007;104(38):15069-74. PMID: 17724330. PMCID: PMC1986614.
- Margolske RF, et al. *Proc Natl Acad Sci USA* 2007;104(38):15075-80. PMID: 17724332. PMCID: PMC1986615.
- (E/I) (NIDCD, NIA)

Grape Seed Extract May Help Neurodegenerative Diseases: Tauopathies—a group of neurodegenerative conditions such as Alzheimer's disease—have been linked to the build-up of "misfolded" tau proteins in the brain. (Tau proteins are associated with microtubules, which help to regulate important cellular processes.) In light of previous studies indicating that grape-derived polyphenols may inhibit protein misfolding, an NIH-funded research center examined the potential role of a particular grape seed polyphenol extract (GSPE) in preventing and treating tau-associated neurodegenerative

disorders. In one study, the researchers found that this GSPE reduced Alzheimer's-type neuropathology and cognitive decline in a mouse model of Alzheimer's disease and inhibited an Alzheimer's-linked process called cerebral amyloid deposition. In another study, the researchers used a variety of analytical techniques to clarify further how the GSPE produces its effects. The results of their preclinical study showed that GSPE interferes with the generation of tau protein aggregates and also disassociates preformed aggregates. Thus, GSPE may affect processes critical to the onset and progression of neurodegeneration and cognitive dysfunctions in tauopathies. The studies' findings, together with indications that this GSPE is likely to be safe and well-tolerated in people, support further exploration and development of GSPE as a therapy for Alzheimer's disease.

- Ho L, et al. *J Alzheimers Dis* 2009;16(2):433-9. PMID: 19221432. PMCID: PMC2800939.
- Ono K, et al. *J Biol Chem* 2008;283(47):32176-87. PMID: 18815129. PMCID: PMC2583320.
- Wang J, et al. *J Neurosci* 2008 Jun 18;28(25):6388-92. PMID: 18562609. PMCID: PMC2806059.
- For more information, see <http://nccam.nih.gov/research/results/spotlight/031209.htm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NCCAM)

Cell and Molecular Biology

Basic Research on Human Embryonic Stem Cells: Research on human embryonic stem cells (hESC) promises to elucidate critical events in early human development and may revolutionize customized regenerative medicine. Since FY 2007, NIH has funded five Program Projects on the basic biology of hESC and has developed initiatives to support fundamental research on a new kind of stem cell, called induced pluripotent stem cells (iPS). iPS cells are reprogrammed from adult cells to a pluripotent state remarkably like hESC. These reprogrammed cells offer a powerful approach to generating patient specific stem cells that ultimately may be used in the clinic. NIH sponsored the third in a series of workshops on research and future directions in human embryonic stem cell research in September 2009.

- For more information, see <http://www.nigms.nih.gov/Initiatives/StemCells>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIGMS)

Scientists Demonstrate Hematopoietic Stem Cells' Role in Forming the Stem Cell Niche: Stem cells are important in all multicellular organisms because they have the ability to develop into different kinds of specialized cells. Outside of the organism, researchers can grow stem cells in specific cultures and observe the development of specialized cells. Blood-forming stem cells, known as hematopoietic stem cells (HSCs), are controlled by the hematopoietic stem cell niche, which is located in the bone marrow. Bone-forming cells called osteoblasts are known to play a central role in establishing the HSC niche; however, it is unclear whether HSCs in turn control the differentiation of stem cells that become osteoblasts. Although such interactions in the niche have been proposed, at present there is insufficient direct experimental evidence to define the relationship between HSCs and osteoblast formation. In this work, a group of investigators addressed the role of HSCs in the differentiation of osteoblasts. Using mice, they co-cultured HSCs with stem cells that become osteoblasts, and demonstrated that HSCs can indeed affect the differentiation of cells into osteoblasts. Further, the investigators found that the specialization or differentiation into osteoblasts could be influenced by the age and physical condition of the mice. These findings suggest that HSCs may serve as an important therapeutic target for controlling bone formation and repair. In particular, it should be possible to develop therapeutic agents that specifically target HSCs for treatment of a variety of bone defect such as osteoporosis, nonhealing bone and tooth defects, and congenital bone abnormalities.

- Jung Y, et al. *Stem Cells* 2008;26(8):2042-51. PMID: 18499897.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDCR)

Molecular Biology and Basic Research

Stem Cells and Regenerative Medicine: Stem cells are able to renew themselves and generate progeny that differentiate into more specialized cells. They play critical roles in organism development, and some are essential for normal homeostasis and tissue repair. NIH has made a significant investment in stem cell research. One NIH-supported study showed that the sex of cells in a subpopulation of muscle-generating stem cells in adult mice can influence their capacity to repair tissue considerably. This finding could lead to future therapies for various diseases, including muscular dystrophy. A collaboration between NIH Intramural researchers and those at Walter Reed Army Medical Center discovered that waste tissues from surgery, removed to promote healing of orthopaedic injuries and war-traumatized muscle, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells. They could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest cells. NIH has partnered with the Department of Defense on an initiative to speed treatments to wounded soldiers abroad, and civilian trauma victims and burn patients in the United States. This collaboration has resulted in the establishment of the new Armed Forces Institute of Regenerative Medicine (AFIRM). The AFIRM-led program will focus on regrowing fingers, repairing shattered bones, and restoring skin to burn victims with genetically matched skin, to pave the way for commercial products in the near future. Hair follicles are useful models for organ regeneration. Recent discoveries have been made in the molecular processes that govern the growth of hair follicle stem cells, which are a source for newly formed hair follicles.

- Deasy BM, et al. *J Cell Biol* 2007 Apr 9;177(1):73-86. PMID: 17420291. PMCID: PMC2064113.
- Jackson WM, et al. *J Tissue Eng Regen Med* 2009 Feb;3(2):129-38. PMID: 19170141.
- Plikus MV, et al. *Nature* PMID: 18202659. PMCID: PMC2696201.
- Horsley V, et al. *Cell* 2008 Jan 25;132(2):299-310. PMID: 18243104. PMCID: PMC2546702.
- Nesti LJ, et al. *J Bone Joint Surg Am* 2008;90(11):2390-8. PMID: 18978407. PMCID: PMC2657299.
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cell_sex_and_stem_cell.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/progenitor_cells.asp
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
- (E/I) (NIAMS, NIA, NIAID, NIBIB)

NIH Stem Cell Task Force: In 2002, NIH established a Stem Cell Task Force to continually monitor the state of this rapidly evolving area of science. The purpose of the Task Force is to enable and accelerate the pace of stem cell research by identifying rate-limiting resources and developing initiatives to overcome these barriers to progress. The Task Force seeks the advice of scientific leaders in stem cell research about moving the stem cell research agenda forward and exploring strategies to address the needs of the scientific community. Since 2002, under the leadership of the Task Force, NIH has supported a wide array of scientific programs designed to foster research on all types of stem cells, including human embryonic stem cells (hESCs), and actively is working to fund research in this blossoming field. For example, the Task Force has stimulated NIH-supported research by initiating Infrastructure grants to scale-up and characterize the hESCs eligible for Federal funding under prior presidential policy, established a National Stem Cell Bank to make these hESC lines readily available, developed training courses to teach stem cell culture techniques, and encouraged new investigator-initiated research through various means. The Task Force also is responsible for implementing Executive Order (EO) 13505, issued by President Obama on March 9, 2009. EO 13505 authorizes the Secretary of Health and Human Services, through the Director of NIH, to support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law. The NIH Guidelines for Human Stem Cell Research were issued on July 7, 2009.

- For more information, see <http://stemcells.nih.gov/policy/taskforce/>
- For more information, see <http://stemcells.nih.gov/policy/2009guidelines.htm>
- (E/I) (NIDCD, NINDS, FDA, NCI, NCR, NHLBI, NIDCR, NIDDK, NIGMS, OD, OER, ORWH, OSP/OSPA)

Bone Marrow Stromal Cells Help Fight Sepsis: Sepsis is a serious medical condition that affects 18 million people per year worldwide, and is characterized by a generalized inflammatory state caused by bacterial infection. Widespread activation of inflammation and blood clotting pathways leads to multiple organ failure, collapse of the circulatory system (septic shock), and death. In the last few years, it has been discovered that bone marrow stromal cells (BMSCs, also known as mesenchymal stem cells) are potent modulators of immune responses. In this study, BMSCs were administered before or shortly after inducing sepsis by puncturing the intestine to determine whether BMSCs injected into the circulation would have a beneficial effect in preventing or attenuating septic shock. Infusion of BMSCs significantly decreased sepsis-induced mortality and increased organ function in an animal model. The effects appear to be mediated by the production of Prostaglandin E2 when BMSCs are activated during the early stages of sepsis. Prostaglandin E2 subsequently induces the recipient's macrophages to produce substantially more IL-10, a factor that dampens the inflammatory response, which if left unabated, leads to death. This is the first determination of a mechanism by which BMSCs modulate the immune response in an animal model of sepsis. As many people die of sepsis annually as die from heart attacks. A new treatment or preventative regimen desperately is needed. Since the animal model suggests that the BMSCs need not be isolated from the same individual as will receive them, it is possible that cells isolated from nonrelated donors could be prepared and stored for use in patients with high risk for sepsis.

- Nemeth K, et al. *Nat Med* 2009;15(1):42-9, PMID: 19098906. PMCID: PMC2706487.
- For more information, see <http://www.nature.com/nm/journal/v15/n1/abs/nm.1905.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Technology Development*
- (I) (NIDCR)

Effects of Storage on Transfused Red Blood Cells: In 2009, NIH initiated a basic and translational research program to identify the molecular and cellular changes that occur during red blood cell unit preparation and storage and to evaluate the effects of storage lesion elements from red blood cell units on the blood vessel wall, host cells, and tissue oxygenation. Recent data suggest that liberal blood transfusions in certain settings are associated with an increase in morbidity and mortality compared to more restrictive strategies, and that transfusion of blood stored for longer periods of time may not be as beneficial as transfusion of "fresher" blood. This program should provide information for improving red blood cell transfusion therapy and clinical outcomes in transfusion recipients.

- (E) (NHLBI)

Smart Coatings for Implanted Biomaterials: A major limitation on the longevity of vascular grafts and implanted materials stems, not from failure of the graft or material itself, but typically, from the body's rejection in the form of blood clots or refusal to integrate with surrounding tissue. Recently, new classes of polymer-based biomimetics that resemble the cell surfaces of healthy blood vessels have demonstrated excellent resistance to platelet adhesion, a major problem for implanted materials in contact with blood. These biomimetic polymers have undergone successful preliminary clinical testing, and the same approach now is being used to develop biomimetic coatings resembling other types of human tissue. This technology recently was acquired by a major medical implant manufacturer.

- Kumar AM, et al. *J Am Chem Soc* 2008;130(4):1466-76. PMID: 18177047. PMCID: PMC2536642.
- Larsen CC, et al. *Biomaterials* 2007;28(24):3537-48. PMID: 17507089. PMCID: PMC2034336.
- This example also appears in Chapter 3: *Technology Development*
- (E) (NIBIB)

Molecular Biology and Basic Research

New Therapeutic Target for Macular Degeneration and Diabetic Retinopathy Discovered: Neovascularization is the term used to describe the growth of abnormal new blood vessels. In some diseases, such as age-related macular degeneration or diabetic retinopathy, neovascularization mistakenly activates and becomes a major pathologic feature. The abnormal vessels leak fluid and serum, which damages the light-sensitive photoreceptor cells in the retina, causing severe and irreversible vision loss. NIH-sponsored research is focused on understanding the pathways that inhibit and promote neovascularization. Previous studies have established that a protein called vascular endothelial growth factor (VEGF) spurs neovascularization, and several therapies have been developed to prevent the abnormal activation of VEGF. A recent NIH-supported study reported the discovery of Roundabout4 (Robo4), a protein that stabilizes the existing vasculature and prevents neovascularization by inhibiting VEGF activity. Robo4 is among a family of Roundabout proteins that previously were found to act as guidance receptors for developing neurons in the nervous system. That Robo4 plays a different and central role in controlling neovascularization represents a breakthrough that may lead to new treatments to prevent or delay the sight-threatening consequences of vascular eye diseases.

- Jones CA, et al. *Nat Med* 2008;14(4):448-53. PMID: 18345009.
- For more information, see <http://www.nature.com/nm/journal/v14/n4/full/nm1742.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NEI)

Cell Senescence and Aging: Cell senescence is a mechanism prominent in aging processes and widely considered as an anti-cancer preventive or treatment therapy. Studies focus on such topics as senescence induced by the Ras gene and its potential to halt or slow tumor progression, the role of the retinoblastoma protein pRb in cellular senescence and the development of a wide range of cell types and associated tumors, telomere attrition, the role of oxidative stress, epigenetic regulation, and DNA damage and repair. NIA-supported studies on Werner syndrome (a condition characterized by accelerated aging in children) and the role of the WRN protein in telomere metabolism are improving our understanding of basic cellular mechanisms that act to suppress development of specific aging characteristics and cancer.

- This example also appears in Chapter 2: *Cancer* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E/I) (NIA)

Cooperative Study Group for Autoimmune Disease Prevention: The Cooperative Study Group for Autoimmune Disease Prevention (CSGADP) was established in 2001 by NIH and its cosponsor the Juvenile Diabetes Research Foundation International as a collaborative network of investigators who focus on understanding immune system dysfunctions that contribute to the development of autoimmune disease (AD), with an emphasis on type 1 diabetes. NIH renewed the Study Group in 2006. It consists of six participating centers that support preclinical research, innovative pilot projects, and clinical studies. Of note, the centers initiated and supported the "Roadmap to Inflammation in the NOD (nonobese diabetic) Mouse" project to identify and characterize genes and proteins involved in the development of diabetes, and study the mechanisms by which diabetes develops. One notable finding suggested by this study is that the development of type 1 diabetes can be characterized by specific differences in how normal genes and gene variants are turned on and off during disease progression. In addition, researchers found patterns of coordinated gene expression that may prove useful as biomarkers of disease onset or progression. Another study, in press, identifies an unusual form of a gene whose expression in specific immune system tissues is associated with type 1 diabetes in both mice and humans.

- Kodama K, et al. *Clin Immunol* 2008;129(2):195-201. PMID: 18801706. PMCID: PMC2592195.
- For more information, see http://fathmanlab.stanford.edu/roadmap_study_design.html
- This example also appears in Chapter 2: *Autoimmune Diseases*
- (E) (NIAID, NIDDK)

Basic Research on Type 1 Diabetes: NIH vigorously supports basic research on type 1 diabetes. For example, the Beta Cell Biology Consortium (BCBC) collaboratively pursues research relevant to the development of therapies for type 1 and type 2 diabetes, including studying pancreatic development, exploring the potential of stem cells as a source for making islets, and determining mechanisms underlying beta cell regeneration (cells that are the source of insulin production). The BCBC has generated research resources, such as animal models and antibodies, which are available to the scientific community. NIH also has launched initiatives to develop artificial pancreas technology for people with type 1 diabetes. One initiative solicited proposals from the small business community on the development of new technologies to advance progress toward an artificial pancreas. NIH also launched the Type 1 Diabetes Pathfinder Awards, to fund new investigators pursuing innovative research on type 1 diabetes and its complications. Research supported through this program focused on areas such as cell replacement therapy, islet encapsulation, and diabetic wound healing.

- For more information, see <http://www.betacell.org>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-001.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-08-012.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-08-013.html>
- For more information, see http://www2.niddk.nih.gov/Funding/FundingOpportunities/RFA/RFA_T1D_Pathfinder_Announcement.htm
- This example also appears in Chapter 2: *Autoimmune Diseases*
- (E) (NIDDK, NIBIB, NICHD)

Lupus: There have been significant advances in identifying disease risk genes for systemic lupus erythematosus (lupus) in recent years. Genome-wide association, linkage analysis, and direct sequencing have revealed genetic variations in lupus patients for molecules involved in immune mechanisms and regulation, inflammation, and vascular cell activities. The disease affects women disproportionately, with female lupus patients outnumbering males nine to one. African American women are three times as likely to get lupus as Caucasian women, and it also is common more in Hispanic, Asian, and American Indian women. These results are being replicated in distinct racial and ethnic populations. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects. Another critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by government agencies, private foundations, and industry. The numerous genes uncovered in these studies reflect the complex expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene specifically is associated with severe forms of lupus that include kidney disease, but not skin manifestations. Methods to analyze patients' blood samples are being developed to group disease-specific variations in gene expression according to pathogenic mechanisms. This system may be used to predict flares of lupus activity in the future and guide individualized treatment. Lupus risk genes also have been discovered on the X chromosome and reproduced in animal models of the disease. These important findings shed light on the female predominance of lupus.

- Edberg JC, et al. *Hum Mol Genet* 2008 Apr 15;17(8):1147-55. PMID: 18182444.
- Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
- Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
- International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), et al. *Nat Genet* 2008;40(2):204-10. PMID: 18204446.
- Taylor KE, et al. *PLoS Genet* 2008;4(5):e1000084. PMID: 18516230. PMCID: PMC2377340.
- Chaussabel D, et al. *Immunity* 2008;29(1):150-64. PMID: 18631455. PMCID: PMC2727981.
- Smith-Bouvier DL, et al. *J Exp Med* 2008;205(5):1099-108. PMID: 18443225. PMCID: PMC2373842.
- Scofield RH, et al. *Arthritis Rheum* 2008;58(8):2511-7. PMID: 18668569.
- Jacob CO, et al. *Proc Natl Acad Sci U S A* 2009;106(15):6256-61. PMID: 19329491. PMCID: PMC2669395.
- This example also appears in Chapter 2: *Autoimmune Diseases*, Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Genomics* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NIAMS, NCI, NCRR, NHLBI, NIAID, NIDCR, NINDS)

Molecular Biology and Basic Research

Asthma Exacerbations: In FY 2005, NIH began a basic and clinical research initiative to improve understanding of the causes of asthma exacerbations and to facilitate the development of more effective treatments to control asthma symptoms. Twelve projects have been funded under this initiative. NIH is assessing the progress of the initiative through an ongoing GPRA goal—"to identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating exacerbations, by 2014."

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-04-029.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NHLBI) (GPRA)

Understanding the Progression from a Skin Disorder to Asthma in Children: NIH-funded researchers investigating basic biochemical mechanisms involved in development have discovered a mechanism that can explain how 50-70 percent of young children affected with the skin rashes of atopic dermatitis (a type of eczema) eventually become asthmatic. The process involves the overproduction of a specific signaling molecule by inflamed skin cells that can trigger the hypersensitivity characteristic of asthma in lung cells. This mechanism and possible ways to prevent this "atopic march" and the development of asthma in general are being actively evaluated in animal models as well as in early human studies.

- For more information, see <http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1000067>
- This example also appears in Chapter 3: *Genomics*
- (E) (NIGMS)

Immunological Factors in Autoimmune Disease: T Helper Cells: T helper cells are a category of immune cells that orchestrate many complex mechanisms in the immune system by receiving molecular signals and, in return, releasing other molecules that control activities of other cells. As a result, these recipient cells are stimulated, or inhibited, from damaging tissues or destroying pathogenic invaders. Studies in recent years have identified a number of T helper cell (Th) subsets that have fairly specific responses to immune system molecules, and are pivotal to attacks against pathogens, as well as autoimmune reactions—when the immune system aberrantly attacks the body it is supposed to protect. NIH-supported researchers have found that one Th subset (Th17) releases molecules that start a cascade of inflammatory events. The effects of Th17 and other pro-inflammatory cells are balanced by another Th subset, T regulatory cells (Tregs), which dampen inflammation. Job's syndrome is a rare immune disorder, characterized by recurrent and often severe bacterial and fungal infections. Due to a genetic mutation affecting a complex biochemical pathway, patients with Job's syndrome lack interleukin 17 (IL17), the molecule that stimulates Th17 cells. As a result, their immune systems fail to protect them from infections, which have the potential to become life-threatening. On the other hand, patients with psoriasis, an autoimmune skin disease, have high levels of IL17 and very active Th17 cells, which drive inflammation in the skin, leading to scaly, damaged tissue. Additional studies have revealed ways that the body might inactivate Tregs. By understanding the details of failures in biochemical pathways in disease states, scientists may begin to identify ways to correct them therapeutically.

- Lowes MA, et al. *J Invest Dermatol* 2008;128(5):1207-11. PMID: 18200064.
- Milner JD, et al. *Nature* 2008;452(7188):773-6. PMID: 18337720.
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2008/job_ma.htm
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2008/08_13b.asp
- This example also appears in Chapter 2: *Autoimmune Diseases*
- (E/I) (NIAMS, NCRR)

New Program to Focus on Better Defining Human Immune Profiles: In 2009, NIH requested applications for a new research program designed to build on recent advances in immune profiling to measure the diversity of human immune responses to infection or vaccination. Grantees will use a variety of modern analytical tools that will define molecular signatures of specific infections, vaccines, or immune adjuvants, as well as describe steady-state human immune status by a number of parameters. This program is a critical component of the NIH immunology research portfolio. This initiative supports studies that characterize human immune cells and their products isolated from diverse subsets of the population after vaccination, infection, or treatment with adjuvants. NIH will create a grantee consortium that will develop and manage a comprehensive database that consolidates and disseminates information for the scientific community and develop new assays and bioinformatics tools to facilitate productivity. This program, originally intended as an FY 2011 initiative, began 1 year early with ARRA funding.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-040.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Autoimmune Diseases*
- (E) (NIAID) (ARRA)

Solving One of Immunity's Puzzles: NIH scientists recently identified a protein required for the crucial interactions between T and B cells that lead to production of antibodies and long-lasting immunity to infectious diseases. T cells and B cells interact to form cellular centers, where B cells proliferate and produce antibodies to fight off invading microbes. This process is crucial to normal immune function and resistance to infectious disease. Researchers demonstrated that a protein, SAP, mediates interactions between T and B cells. Specifically, the team found that T cells lacking SAP do not bind strongly to the B cells they would otherwise recognize. This in turn prevents B cells from receiving crucial signals they need to help build antibody-secreting cells. This malfunction leads to the poor immune response observed in patients with X-linked lymphoproliferative disease, a rare disorder affecting newborn boys.

- Qi H, et al. *Nature* 2008;455(7214):764-9. PMID: 18843362. PMCID: PMC2652134.
- For more information, see <http://www.genome.gov/27528397>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E, I) (NHGRI, NIAID)

Developing New Adjuvants to Boost Vaccine Effectiveness: Adjuvants activate the body's innate immune system, a prerequisite for effective responses by the adaptive immune system—antibody-producing B cells and antigen-specific T cells. In 2004, NIH launched the "Innate Immune Receptors and Adjuvant Discovery" initiative in response to the growing need to boost the effectiveness of vaccines against potential agents of bioterrorism and emerging infectious diseases. The initiative encouraged the discovery of novel adjuvants that stimulate the innate immune response through proteins known as pattern recognition receptors, which the innate immune system uses to identify microbial pathogens. To build on the success of this program, NIH initiated the Adjuvant Development program in 2008. Four groups were funded to advance identified adjuvants toward licensure for human use in vaccines against diseases such as influenza and tuberculosis, as well as infection with West Nile virus. The "Innate Immune Receptors and Adjuvant Discovery" initiative was reissued—inviting new grant applications—in FY 2009 to continue the generation of potential adjuvant candidates. The research focus on adjuvants yielded a major science advance in 2008 when several groups of NIH-supported investigators discovered that alum activates the innate immune system by stimulating clusters of proteins called inflammasomes, found inside certain cells. This new information should provide keys to better understanding adjuvant function and should facilitate the design of new vaccine adjuvants.

- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2008/alum_vaccine.htm
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIAID)

Molecular Biology and Basic Research

Improving Transplantation Outcomes: Organ transplantation prolongs survival and greatly improves quality of life for children and adults suffering from a wide range of congenital and acquired diseases. Yet, despite advances in transplantation, normal life expectancy and health-related quality of life are not restored fully by organ transplantation. To improve the outcomes of organ transplantation, NIH supports the Clinical Trials in Organ Transplantation (CTOT) initiative, a cooperative, multisite consortium to develop and implement interventional and observational clinical studies, accompanied by mechanistic studies.

In one notable CTOT study, NIH-supported investigators developed a regimen that included transplantation of both kidney and bone marrow from the same donor and use of immunosuppressive therapies prior to and just after transplantation. Nine to 14 months after the transplant, investigators were able to discontinue all immunosuppressive medications with this regimen in four of the five patients, without subsequent rejection of the kidney. In another study, NIH-supported investigators studied whether acute graft rejection was associated with changes in the expression of genes involved with the adaptive immune response. They measured levels of microRNAs in healthy transplanted kidneys and in transplants undergoing rejection. The team found a pattern of six microRNAs that could distinguish healthy kidneys from those in the process of being rejected. These results suggest that microRNAs may be a useful measurement for assessing human kidney transplant status. If the rejection signature appears early enough, doctors one day may be able to treat patients before organ damage occurs and to better tailor immunosuppressive therapy to the individual patient.

- Kawai T, et al. *N Engl J Med* 2008 Jan 24;358(4):353-61. PMID: 18216355. PMCID: PMC2819046.
- For more information, see <http://www.immunetolerance.org/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIAID, NHLBI, NIDDK)

'Omics' Approaches

Discovery of Novel Epigenetic Marks in Mammalian Cells: The NIH Roadmap Epigenomics Program aims to accelerate the promise of epigenetics into applications that affect human health and a wide range of common complex human diseases by fostering the development of novel resources for research in this field. Epigenetics refers to various modifications to DNA, its associated proteins, or overall chromosome structure that influence whether genes are active or silent, independent of the DNA sequence. Research supported by this program will characterize the "epigenome," a catalog of the stable epigenetic modifications or "marks" that occur in the genome (and which may differ in different types of cells) and its impact on health and disease. One component of the program is an initiative to support research to identify novel epigenetic marks in mammalian cells and assess their role in the regulation of gene activity. It is anticipated that the results of these studies will be translated quickly to global epigenome mapping in human cells (conducted by the Epigenomics Roadmap Program's Reference Epigenome Mapping Centers). The eight research grants funded by this component of the program are expected to yield results that could have a significant impact on our understanding of gene regulation in mammals. In the long term, advances in these areas will enhance our ability to investigate, diagnose, and ameliorate human disease with a significant epigenetic component. For instance, NIH plans to build on these studies to examine the role of epigenomics in diabetes complications and to study effects of the intrauterine environment on the development of diabetes. Other research will examine epigenetic markers of beta cell differentiation.

- For more information, see <http://nihroadmap.nih.gov/epigenomics/initiatives.asp>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Genomics*
- (E) (NIDDK, Common Fund - all ICs participate)

Regulation of Gene Expression by Chemically Marking DNA: Studies by NIH intramural scientists of how genes are turned on (expressed) or off have provided insight into gene regulation and the overall organization of the genome. For example, a recent study indicated the importance of a mammalian protein called Vezf1 in maintaining the integrity of the genome. This protein previously had been identified by research on an "insulator" element—a segment of DNA that marks boundaries in the genome and allows neighboring genes to be regulated independently. Research on insulator elements—found in fruit flies, chickens, and mammals—has provided great insight into the molecular mechanisms used by the cell to turn on certain genes while keeping other genes turned off. In studies of Vezf1, the scientists discovered that deletion of the gene encoding the Vezf1 protein in a mouse embryonic stem cell line led to loss of specific chemical marks on the DNA at widespread sites in the genome. This type of chemical mark, known as DNA methylation, is a signal used by the cell to turn a gene off. The scientists also demonstrated that the loss of DNA methylation observed when Vezf1 was deleted was due to a decrease in the amount of a specific protein that puts this mark on the DNA. Therefore, Vezf1 is required for the DNA methylation pattern in these cells. Continued studies of insulators and their associated proteins will lead to further understanding of the regulation of genes, an essential process for health and development.

- Gowher H, et al. *Genes Dev* 2008;22(15):2075-84. PMID: 18676812. PMCID: PMC2492749.
- This example also appears in Chapter 3: *Genomics*
- (I) (NIDDK)

Scientists Accomplish Initial Catalogue of the Human Salivary Proteome: Secretions from the major salivary glands (parotid, submandibular, and sublingual) contain many peptides and proteins. They contribute to saliva's important roles in maintaining oral health, including antimicrobial, lubricating, buffering, and digestive properties. Salivary gland disorders, which result in severe dry mouth, compromise quality of life because they often lead to decay and periodontal diseases, mucosal infections, halitosis, taste impairment, and difficulties in swallowing and speaking. Saliva is a complex fluid; over the years, a number of salivary proteins have been reported but a systematic approach to catalogue all the proteins present in saliva was only initiated in 2004. NIH supported three teams of investigators to conduct the first comprehensive analysis of the salivary proteome. After samples were collected and analyzed, the data were standardized and integrated, yielding a salivary proteome that comprises 1,166 proteins. Of these proteins, 152 parotid and 139 submandibular/sublingual proteins were identified by all 3 research groups; these proteins form the core proteome. Most proteins identified were extracellular or secretory proteins, and involved in numerous molecular and cellular processes. A significant number of proteins represented in the salivary proteome also have been found to exist in the plasma or tear proteomes. This initial catalogue of the salivary proteome is a significant first step toward a comprehensive understanding of what the functions of saliva are, and how salivary composition is dependent on physiological variations, including on health and disease. This proteome could be the source of potential diagnostic and prognostic biomarkers for oral and systemic conditions.

- Denny P, et al. *J Proteome Res* 2008;7:1994-2006. PMID: 18361515.
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*
- (E) (NIDCR)

Study Finds Unexpected Bacterial Diversity on Human Skin: One of the NIH Roadmap initiatives, the Human Microbiome Project (HMP) is a trans-NIH program that aims to expand upon traditional microbiology and discover what microbial communities exist in different parts of the human body and how they might change with disease. In a healthy adult, microbial cells far outnumber those of the human host, but remarkably little has been known until now about how these microbes behave in the body. HMP makes use of a metagenomic approach that reveals data about entire human-associated microbial communities. In 2009, data gathered by a trans-NIH team revealed unexpected bacterial diversity on human skin that, it is hoped, will lead to advances in understanding a range of disorders, such as eczema, psoriasis, and acne.

Molecular Biology and Basic Research

- Grice EA, et al. *Science* 2009;324(5931):1190-2. PMID: 19478181.
- For more information, see <http://nihroadmap.nih.gov/hmp/index.asp>
- This example also appears in Chapter 3: *Genomics*
- (I) (NHGRI, Common Fund - all ICs participate, NCI)

Glycomics Technology Development, Basic Research, and Translation into the Clinic: Glycans are ubiquitous complex carbohydrates found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules is thus critical for basic and clinical research across the spectrum of health and disease, but widely is regarded as one of the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- Biomedical Technology Research Centers develop and share cutting-edge technologies for analysis of carbohydrates in complex biological systems.
- Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.
- Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
- A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.

- For more information, see <http://www.ncrr.nih.gov/glycomics>
- For more information, see <http://www.functionalglycomics.org>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
- (E) (NCRR, NCI, NHLBI, NIGMS, NINDS)

Reference Epigenome Mapping Centers: The Reference Epigenome Mapping Centers (REMCs), one of the Roadmap Epigenomics initiatives, are developing resources in reference epigenomes that the field has been requesting for the last 5 years, as indicated by recommendations made at several workshops and conferences focused on epigenetics and human health and disease. The funded centers form a network collaborating to provide comprehensive maps of all known epigenetic marks across a set of mutually agreed-upon reference cell types. This consortium, with input from advisors, will identify the most appropriate cell populations and determine standardized methods for growing or acquiring the cells so that data can be compared and integrated maps can be generated. The network of REMCs will produce comprehensive, high resolution, experimental data on epigenetic marks in specific cell populations, such as high-quality, pluripotent human embryonic stem cells, other human differentiating stem cells, and differentiated cell types including human cell types relevant to complex diseases of high public health significance. In addition, it will provide an informatics pipeline to generate high-quality reference epigenome maps from the centers' data; facilitate additional data analyses, in collaboration with the Epigenome Data Analysis and Coordinating Center, to integrate data from maps generated by REMCs from a specific cell type for different epigenetic marks; and conduct ancillary studies to develop limited data on functional aspects of epigenetic control of gene activity.

- For more information, see <http://nihroadmap.nih.gov/epigenomics/>
- For more information, see <http://cancerres.aacrjournals.org/cgi/reprint/65/24/11241>
- For more information, see <http://www.landesbioscience.com/journals/epigenetics/article/heindelEPI1-1.pdf>
- This example also appears in Chapter 3: *Genomics*
- (E) (NIEHS, NIDA, Common Fund - all ICs participate)

Systems Biology

Systems Biology and Systems Genetics: The Integrative Cancer Biology Program (ICBP) provides new insights into the development and progression of cancer as a complex biological system. Teams of researchers at ICBP Centers are integrating the disciplines of biology, medicine, engineering, math, and computer science (e.g., computational biology). ICBP Centers use a spectrum of innovative technologies such as genomics, proteomics, and molecular imaging to generate and validate computational and mathematical models. These *in silico* models describe and simulate the complex process of cancer, from the basic cellular processes through tumor growth and metastasis, and allow researchers to run "virtual" experiments, which ultimately should lead to better cancer prevention, diagnostics, and therapeutics. The centers have produced more than 35 computational models, developed a validated siRNA library of cancer genes, and created a set of nationally distributed breast cancer cell lines that reflect the heterogeneity of human breast cancer. Equally important to our understanding of cancer is systems genetic research (systems biology + genetics). Networks of genes can be found and their associations tested and quantified with parallel association studies on relevant human populations.

- For more information, see <http://icbp.nci.nih.gov/>
- This example also appears in Chapter 2: *Cancer*
- (E) (NCI)

National Centers for Systems Biology: Systems biology promotes tight integration of experimental and computational approaches to solving complex problems. Currently, NIH-funded researchers at 10 interdisciplinary Centers are using computational modeling and analysis to study the complex dynamics of molecular signaling and regulatory networks involved in cell proliferation, differentiation, death, and response to environmental changes; developmental pattern formation in organisms; genome organization and evolution; and drug effects on cells, organs, and tissues. The Centers advance their research fields and provide training for the next generation of computationally skilled scientists.

- For more information, see <http://www.nigms.nih.gov/Initiatives/SysBio>
- (E) (NIGMS)

Computational Modeling of Regulatory Processes: Phosphorylation, the addition of a phosphate group to a protein or other molecule, is a common mechanism of cellular processes. Proteins may contain more than 1 site of phosphorylation, and, interestingly, many key regulatory proteins are phosphorylated at 10 or more different sites. NIH-funded researchers recently have introduced novel methods, based in the sophisticated branch of mathematics known as "algebraic geometry," into a computational model of phosphorylation, giving them a new technique to explore a variety of processes related to cancer and other diseases. This advance exploits a mathematical construct named for the Austrian mathematician Wolfgang Grobner (1899-1980), and demonstrates how long-established findings in fields such as abstract mathematics can be brought to bear in the context of biological research. In this case, the mathematics allows the computational biologists to work around putting a precise numerical value to every detail of the model, thus greatly simplifying their efforts to perform computational experiments. It is anticipated that these simplifying methods, based on an area of mathematics previously far removed from work in the life sciences, will be widely applicable to modeling of many biological processes.

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- (E) (NIGMS)

Metabolic Network Model of a Human Oral Pathogen: The bacterium *Porphyromonas gingivalis* causes severe, chronic periodontal disease. Recently NIH-supported researchers constructed a complex metabolic network map for *P. gingivalis* with which to model the metabolic properties of all genomically identified components of the system. The scientists used a technique known as flux-balance analysis (FBA) to construct the model, which consisted of 679

Molecular Biology and Basic Research

metabolic reactions involving 564 metabolites. There was significant correlation between the model's predictions and the bacterium's experimentally observed metabolism. The true power of this model became apparent when "virtual knockouts" were employed to predict the effect of the loss of certain genes or metabolic pathways on growth rate, and the model very effectively predicted disturbances affecting biosynthesis of large molecules known as lipopolysaccharides. This is the first description of a model of this type for an oral periodontal pathogen. Still in their infancy, metabolic network models are a logical extension of genome sequence data. They can provide the ability to perform virtual metabolic modeling of organisms with limited or no in vivo experimental histories. These models also could be applied to highly interdependent mixed microbial communities, including the oral microbiome, ultimately resulting in new biomedical applications. Such modeling greatly increases opportunities to discover new antibacterial drug targets. These studies provide new molecular targets for therapeutic drugs; they also can suggest the molecular mechanisms for virulence, intracellular persistence and survival, and ability of the bacteria to survive stresses from the (in this case, human) host defense mechanisms.

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- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Technology Development*
- (E) (NIDCR)

Environmental Factors

Centers for Neurodegenerative Science: NIH has awarded three Centers for Neurodegeneration Science program grants to conduct research that combines human studies with basic mechanistic research to understand how environmental factors contribute to the origins, progression, treatment, and prevention of neurodegenerative diseases. The three projects will focus on investigating Parkinson's disease (PD). PD is linked to pesticide exposure, mitochondrial damage, and altered storage of dopamine. One project will look at how environmental and genetic factors interact in PD pathogenesis and search for biomarkers that will help identify people at risk for developing PD. A second project will investigate the importance of the ubiquitin-proteasome system, microtubules, and aldehyde dehydrogenase disruption by pesticides in conferring vulnerability to dopamine neurons. An integrated, multidisciplinary approach will be used to identify agricultural pesticides that are able to disrupt the same cellular pathways shown to alter the viability of dopaminergic neurons and determine whether these pesticides increase the risk of PD. The third project will focus on proteins known to be related to PD with the goal of determining how chemical reactions lead to damaging modifications of these proteins. Clinical implications will be explored through biomarker development and a screen to identify compounds that can preserve protein function by reducing free radical stress. The knowledge generated by these projects will provide therapeutic targets for disease intervention and prevention strategies.

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- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NIEHS)

Environmental Epigenetics: Key Mechanisms for Environmental Effects on Gene Function and Disease: Increasing evidence demonstrates that epigenetic mechanisms—cellular regulatory processes that influence the expression of genes without affecting DNA sequence—play important roles in the pathogenesis of disease. Epigenetic regulation of genes is critically important in normal developmental biology and disease development/progression, and epigenetic modifications

can be influenced by environmental exposures (this may be an important mechanism for gene/environment interactions). An early NIH grant program called Environmental Influences on Epigenetic Regulation has resulted in some groundbreaking research on understanding these processes and their roles in health and disease. We know that environmental exposures early in development affect the risk of diseases and dysfunctions that occur in adulthood, many years later. Evidence is growing that exposures *in utero* exert their effects through epigenetic modifications such as DNA methylation (a chemical change to DNA that is associated with silencing gene expression). A recent study in yellow agouti mice demonstrated that maternal exposure to bisphenol A shifted the coat color of the offspring by decreasing methylation in a regulatory portion of the DNA sequence upstream of the coat-color gene. Moreover, maternal dietary supplementation with either folic acid or a phytoestrogen (genistein) inhibited the ability of bisphenol A to reduce DNA methylation. These and other results highlight the importance of this growing area of research for our ability to understand developmental pathogenesis and to design effective interventions.

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- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIEHS)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects

Molecular Biology and Basic Research

adipose tissue and alters hormonal control of sexual maturation. Endocrine disruptors, irradiation, and psychosocial elements also will be studied for effects.

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- For more information, see <http://www.bccrc.org/>
- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Genomics* and Chapter 3: *Clinical and Translational Research*
- (E) (NIEHS, NCI) (GPRA)

National Toxicology Program/Tox21: Tox21 is a collaboration on the research, development, validation, and translation of new and innovative test methods that will better determine the toxicity of chemicals to which humans are or might be exposed. A central component is the exploration of novel high-throughput screening assays using human cells to evaluate mechanisms of toxicity. Program success will result in toxicity testing methods that are less expensive, provide higher throughput, and are better able to predict toxic effects in humans. As a result, Tox21 will increase the government's ability to evaluate large numbers of chemicals that currently lack adequate toxicological evaluation, while reducing the use of animals in regulatory testing.

- (I) (NIEHS) (GPRA)

Testing for Reproductive Tumors in the National Toxicology Program's Carcinogenesis Bioassay: Perinatal Dosing: The National Toxicology Program (NTP) evaluates substances for a variety of health-related effects. Two-year studies in laboratory rodents remain the primary method by which chemicals or physical agents are identified as having the potential to be hazardous to humans. In 2006, NTP convened a workshop on Hormonally Induced Reproductive Tumors, Relevance of Rodent Bioassays to discuss the adequacy of rodent models used in the 2-year bioassay for detecting reproductive tumors. The workshop recommended that in utero and lactational exposures could be added to the chronic bioassay depending upon what is known about the mode of action. For detecting tumor types such as testicular germ cell tumors, this recommendation was especially strong. In utero and lactational exposures should be considered for mammary tumor studies if there are any developmental effects associated with a substance under study that involved

endocrine tissues, steroid receptor binding, a change in mammary gland morphology, or altered timing of vaginal opening. NTP has conducted such perinatal exposures on cancer bioassays in the past, but only when there was special justification for such a design to be adopted. A new default design in which dosing will start in pregnancy and be continued throughout life or to the end of a 2-year period now has been adopted unless there is a good scientific reason not to undertake such a study. NTP has initiated studies to obtain data for constructing physiologically based pharmacokinetic (PBPK) models in rodents and nonhuman primates. It is planning studies to explore the long-term consequences of perinatal exposure to Bisphenol A to understand the potential impact to humans of the developmental changes reported in numerous laboratory animal studies. It is hoped that the PBPK models will link information from rodent studies with primate studies, and potentially with human outcomes.

- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (O) (NIEHS)

Mercury and Autoimmunity: The causes of autoimmune diseases remain unknown although genetic and environmental factors are believed to play major roles in susceptibility. NIH supports research projects investigating heavy metal-induced autoimmune diseases. The Mercury Induced Autoimmunity Project is working on the role that interferon-gamma plays in the development of induced murine systemic autoimmunity. Another NIH-supported project is investigating links between mercury (Hg) exposure and autoimmune heart disease. This project will assess programming changes that occur during the innate immune response to infection following exposure to Hg, with an overall effect on the progression of Coxsackievirus-induced autoimmune heart disease in mice, and apply the biomarkers from the studies in animals to a Hg-exposed human population in Amazonian Brazil. Another project is investigating the effect of Hg on the neuroimmune system. Studies will investigate the effects of Hg on production of autoantibodies to brain antigens. Antibodies to brain antigens have been demonstrated in patients with different neurological diseases, including neuropsychiatric lupus, Parkinson's disease, schizophrenia, and autism spectrum disorders. An ongoing project is working on development and uses mouse models to understand the relationships between immune system dysfunction and perinatal exposure to environmental toxicants in the development of neurobehavioral disorders such as autism. Mice from this project will be used to assess the effects of perinatal exposure to low levels of methyl mercury (MeHg) on abnormal brain development and behavior mediated by the immune system. These studies should allow insight into the mechanism of induction of immune dysfunction and point to a possible means of therapeutic intervention.

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- This example also appears in Chapter 2: *Autoimmune Diseases*
- (E) (NIEHS)

Bisphenol A Exposure and Effects: More than 90 percent of the U.S. population is exposed to low levels of BPA. Exposures may occur through use of polycarbonate drinking bottles and the resins used to line food cans. The NIH National Toxicology Program's (NTP's) Center for the Evaluation of Risks to Human Reproduction conducted an evaluation to determine whether current levels of exposure to BPA present a hazard for human reproduction and/or development. Following this evaluation of existing literature, the NTP expressed "some concern" for effects on the brain, behavior, and prostate gland based on developmental effects reported in some laboratory animal studies using BPA exposures similar to those experienced by humans. NIH is working to address and support research and testing needs identified during the NTP evaluation to understand any potential risks for humans from BPA exposure. In collaboration with scientists at the FDA National Center for Toxicological Research, the NTP has designed and begun studies to evaluate similarities and differences in how rats metabolize BPA in relation to nonhuman primates, and to further understand the long-term health consequences from exposures to low levels of BPA during rodent development. In addition, NIH is providing grant support to the extramural community for studies that focus on investigating possible long-term health outcomes from developmental exposure or chronic exposures to environmentally relevant doses of BPA.

Molecular Biology and Basic Research

Collectively, these studies should address research gaps, reduce uncertainties, and provide perspective regarding any potential risk that BPA poses for public health.

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- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (I) (NIEHS)

Basic Behavioral and Social Science Research

NIH Basic Behavioral and Social Science Opportunity Network: NIH Basic Behavioral and Social Sciences Opportunity Network (OppNet) is a new trans-NIH initiative that will identify and support research in the basic behavioral sciences. Basic research in the behavioral and social sciences examines fundamental mechanisms and patterns of behavioral and social functioning. Examples include research on how people remember, how innovative practices spread, and the effects of brain processes on behavior. Basic behavioral and social sciences research (bBSSR) involves both human and animal studies and spans the full range of scientific inquiry, from processes at the intra-individual level ("under the skin"), to mechanisms "outside the skin" that explain inter-individual, group-, organizational-, community-, and population-level patterns of collective behavior. The mission to support basic behavioral science is shared across NIH ICs. Initiated in September 2009, OppNet will provide a means for integrating NIH's assessment of its bBSSR investments, ensuring that opportunities in relevant areas of science are addressed, and that effective mechanisms are in place to advance these sciences. The initiative will support targeted initiatives of general relevance to the NIH mission, drawing from a common pool of funds.

- (E) (NIA, NIGMS, OBSSR, FIC, NCCAM, NCI, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIMH, NINDS, NINR, NLM, OAR, ODP, ORWH)

Facilitating Interdisciplinary Research via Innovation in the Behavioral and Social Sciences: An NIH Roadmap Funding Opportunity Announcement (FOA), *Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences*, was released. Using a modified Exploratory/Developmental (R21) mechanism, this FOA solicits applications to develop new and innovative measures, methods, and technologies that support the integration of human social and/or behavioral science with other disciplines across varying levels of analysis. Supported projects have included: creation of tools to measure sun exposure and vitamin D, models of spinal cord injury, and an Internet-based system for providing feedback to teachers and consultants on the

school readiness and mental health of children. Several national conferences have been planned in relation to this initiative, including *Facilitating Interdisciplinary Research: Methodological and Technological Innovation in the Behavioral and Social Sciences* (October 2009).

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-004.html>
- For more information, see <http://nih.blhtech.com/roadmap09/>
- This example also appears in Chapter 3: *Technology Development*
- (E) (NIDA, OBSSR, Common Fund - all ICs participate)

CISNET—A Resource for Comparative Effectiveness Research: The Cancer Intervention and Surveillance Modeling Network (CISNET) represents a quantum leap forward in the practice of modeling to inform clinical and policy decisions. While contemporary science has enabled the collection and analysis of health-related data from numerous sectors, enormous challenges remain to integrate various sources of information into optimal decision-making tools to inform public policy. Collaborative work on key questions promotes efficient collecting and sharing of the most important data and critical evaluation of the strengths and weaknesses of each resource. Providing results from a range of models, rather than a single estimate from one model, brings credibility to the process and reassures policymakers that the results are reproducible. CISNET is a consortium of NIH-sponsored investigators who use modeling to improve understanding of the impact of cancer control interventions (e.g., prevention, screening, and treatment) on incidence and mortality trends. The consortium's work informs clinical practice and recommended guidelines by synthesizing existing information to model gaps in available knowledge. CISNET provides a suite of models that are poised to determine the most efficient and cost-effective strategies for implementing technologies in the population. Four groups of grantees focus on breast, prostate, colorectal, and lung cancers using statistical simulation and other modeling approaches. Their models incorporate data from randomized controlled trials, meta-analyses, observational studies, epidemiological studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of these interventions.

- For more information, see <http://cisnet.cancer.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (NCI)

Support for Collaborative Science: In FY 2009, NIH launched the Administrative Supplements for Collaborative Science (SCS) program. These supplements are intended to enhance ongoing research by stimulating and supporting new multidisciplinary collaborations among NIGMS grantees and other members of the scientific community. The program has proved to be quite popular. NIH received 217 applications for the three submission dates in FY 2009, and plans to fund at least 32 applications from Institute funds. NIGMS intends to support additional meritorious applications with funds received from the American Recovery and Reinvestment Act of 2009.

- For more information, see <http://www.nigms.nih.gov/Initiatives/Collaborative/SCS.htm>
- (E) (NIGMS) (ARRA)

NIH Committee on the Science of Behavior Change (SOBC): A key national goal, at the scientific and policy level, is to eliminate preventable diseases and their associated disabilities and premature deaths. To achieve this goal, the science of behavior change increasingly is being recognized as a critical area for research. While NIH historically has invested in biobehavioral research, SOBC is a crucial step to coordinate, leverage, and advance these efforts. The SOBC initiative examines topics that span the continuum of behavior change and across disciplines. The SOBC goals include the identification of new and productive paradigms for SOBC research—paradigms that will facilitate the synthesis, integration, and application of SOBC research; that will help to bridge the distances that often separate investigators and

Molecular Biology and Basic Research

disciplines; and that will inform and identify future research directions and initiatives. On June 15-16, 2009, NIH brought together experts in the fields of basic and applied behavioral sciences, genetics, economics, and methodology with the goal of advancing an NIH-wide agenda on the science of behavior change. The main topics of discussion were the acquisition and prevention of behavior, changing existing behavior, and maintenance of behavior. The SOBC working group will use ideas generated from the meeting to develop new interdisciplinary initiatives in behavior change research.

- For more information, see http://nihroadmap.nih.gov/documents/SOBC_Meeting_Summary_2009.pdf
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (NINR, NIA, DPCPSI, FIC, NCCAM, NCI, NHGRI, NHLBI, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIGMS, NIMH, NINDS, OBSSR)

Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging: NIH supports 13 Roybal Centers whose objective is to improve the health, quality of life, and productivity of middle-aged and older people by facilitating translation of basic behavioral and social science to practical outcomes by developing new technologies and stimulating new "use-inspired" basic research in the behavioral and social sciences. Roybal investigators have made several key discoveries. For example: One Center has developed tools and technologies for identifying older adults at risk for automobile crash involvement, and is working with industry partners to develop and disseminate products based on these tools. Another Center has developed two evidence-based interventions from its in-depth work on physical activity for older adults. One program, Fit and Strong!, is targeted to older adults with lower extremity osteoarthritis, and one is targeted to older adults with developmental/intellectual disabilities (primarily Down syndrome). A Roybal investigator has developed instruments for self-efficacy appropriate for use with older adults with developmental/intellectual disabilities; these have been adopted internationally. Finally, a Center has developed a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Other companies have used this model to develop related products, and the model has spurred several new grant-funded research projects, including the development of a new medication tracker for older adults.

- For more information, see <http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/roybals.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
- (E) (NIA)

NIH Revision Awards for Studying Interactions Among Social, Behavioral, and Genetic Factors in Health: NIH issued three program announcements with review (PARs) to support competitive supplements for NIH grantees to study how interactions among genetic and behavioral/social factors influence health and disease. NIH is committing \$7.9 million to support 11 applications submitted in response to these announcements, which will enable the addition of a genetics/genomics component to ongoing behavioral or social science research projects. The knowledge gained by such research will improve our understanding of the determinants of disease as well as inform efforts to reduce health risks and provide treatment.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/par-08-065.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-066.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-067.html>
- For more information, see http://obssr.od.nih.gov/scientific_areas/Genes_Beh_Environ/index.aspx
- This example also appears in Chapter 3: *Genomics*
- (E) (OBSSR, NCCAM, NCI, NEI, NHGRI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIMH, NINDS, NINR, ODP/ODS)

Genes Involved in the Regulation of Sensitivity to Alcohol: Low doses of alcohol are stimulating in both humans and animals while higher doses have sedating effects. Sensitivity to alcohol, however, varies across individuals and low sensitivity to alcohol is a risk factor for the development of alcohol dependence in humans. Research with individuals who have a high family history of alcoholism seeks to understand how low response to alcohol contributes to dependence and how it can be used to predict risk for future alcohol problems. Research with animals is useful in identifying the mechanism(s) underlying the level of sensitivity to alcohol. Recently, a study with fruit flies implicated the Epidermal Growth Factor Receptor (EGFR) signaling pathway in regulating sensitivity to alcohol. Importantly, FDA-approved medications that inhibit EGFR increase alcohol sensitivity in mice and decrease alcohol intake in rats, suggesting that these drugs may offer therapeutic opportunities for treatment of alcohol use disorders in humans.

- Corl AB, et al. *Cell* 2009;137(5):949-60. PMID: 19464045.
- Trim RS, et al. *Alcohol Clin Exp Res* 2009;33(9):1562-70. PMID: 19485971.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIAAA)

The Role of Development in Drug Abuse Vulnerability: NIH supports animal, clinical, and epidemiological research across the lifespan to examine how developmental stage may influence drug abuse vulnerability or protection. The discovery of a protracted period of brain changes during early development and beyond has been critical to understanding the role of brain maturation in decision-making processes and responses to stimuli, including early (e.g., in utero) exposure to drugs. Adolescence has emerged as a particularly vulnerable period, during which an immature brain circuitry can translate into a preponderance of emotional reactivity (vs. higher cognitive control) that gives rise to the impulsive characteristics of many teenagers. This in turn may lead to dangerous risk-taking, such as experimenting with drugs that ultimately can lead to addiction. Using both animal models and clinical research, scientists are beginning to understand how environmental variables can play a key role in shaping brain maturation trajectories. In this regard, imaging, genetic, and epigenetic tools are helping interpret the effects of myriad environmental influences, such as quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics on brain development and behavior. In addition, the field of social neuroscience is harnessing the power of multidisciplinary approaches to tease apart these multilevel phenomena to better understand, for example, the neural mechanisms of peer pressure, the connections between chronic stress and risk of drug abuse initiation, and the impact that different early rearing environments can have on gene expression and behavior.

- For more information, see <http://www.nida.nih.gov/tib/prenatal.html>
- For more information, see <http://www.nida.nih.gov/scienceofaddiction/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIDA, NICHD) (GPRA)

New Genetics/Epigenetic Tools Shed Light on Addiction: NIH-supported research is taking full advantage of expanding databases and fast technologies to identify links between genetic variations and disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms underlying complex diseases like addiction, which genes strongly influence. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as "gene chips" (e.g., the neurexin gene has been found to play a role in drug addiction). Applying these tools to addiction and other brain disorders advances our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient's genetic profile. To complement these efforts, NIH is investing in the equally important field of epigenetics, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the

Molecular Biology and Basic Research

deleterious long-term changes to brain circuits from drug abuse. For example, using a powerful new technique known as ChIP-on-chip to monitor epigenetic changes correlated with gene activity, investigators recently have mapped the genomic effects of chronic cocaine use in the reward center of the mouse brain. Such analyses provide needed information about which genes are altered by cocaine and can point to new targets for medications development. Epigenetic discoveries also can inform ways to smartly alter environmental factors so as to decrease the risk for drug abuse and addiction.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-015.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-016.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-003.html>
- For more information, see <http://nihroadmap.nih.gov/epigenomics/initiatives.asp>
- For more information, see <http://nihroadmap.nih.gov/commonfundupdate.asp>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Genomics* and Chapter 3: *Technology Development*
- (E/I) (NIDA, NCI, NIAAA, NIMH) (GPRA)

A Multidisciplinary Approach to Tobacco Addiction: Tobacco addiction is the number one preventable public health threat, with enormous associated morbidity, mortality, and economic costs. Cigarette smoking—powerfully addictive mainly because of the key ingredient nicotine—is the greatest preventable cause of cancer, accounting for at least 30 percent of all cancer deaths, 87 percent of lung cancer deaths, and nearly 80 percent of deaths from chronic obstructive pulmonary disease, according to CDC. CDC also reports that these leading causes of death could become relatively uncommon in future generations were the prevalence of smoking substantially reduced. In that vein, NIH-supported research has led to major advances in critical areas that together could greatly enhance our ability to either prevent or mitigate the impact of tobacco addiction. Convergent genomic studies recently have uncovered several genes previously not associated with nicotine reward or addiction that convey increased risk for addiction. This finding identifies markers of vulnerability, as well as new targets for medications development, with the potential to personalize, and thereby improve, treatment based on patients' genetic profiles. Clinical trials are exploring new medications and behavioral therapies for tobacco addiction. A promising approach, which already completed Phase II clinical testing, is that of immunotherapy. A nicotine vaccine (NicVAX), which binds nicotine in the blood, preventing it from ever reaching the brain, showed strong positive results in promoting abstinence among study participants who achieved sufficient antibody levels. Further studies are helping to define optimal protocols for vaccination to improve results in all smokers. This may be a particularly useful tool for tobacco cessation programs in the not-too-distant future.

- Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and productivity losses United States, 1997-2001. *Morb Mortal Wkly Rep* 2005;54:625-8.
- Centers for Disease Control and Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses United States, 2000-2004. *Morb Mortal Wkly Rep* 2008;57(45):1226-28.
- Institute of Medicine. *Ending the Tobacco Problem: A Blueprint for the Nation*. Washington, DC: National Academies Press; 2007.
- For more information, see <http://www.drugabuse.gov/ResearchReports/Nicotine/Nicotine.html>
- For more information, see http://cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDA, NCI) (GPRA)

According to a Government Survey, 38 Percent of Adults and 12 Percent of Children Use Complementary and Alternative Medicine: In December 2008, NIH and the National Center for Health Statistics released new findings on Americans' use of complementary and alternative medicine (CAM). The findings are from the 2007 National Health Interview Survey (NHIS), an annual in-person survey of Americans regarding their health- and illness-related experiences.

According to the survey, approximately 38 percent of adults and nearly 12 percent of children use some form of CAM. For both adults and children, the most commonly used type of CAM is nonvitamin/nonmineral natural products, and the most common use for CAM is to treat pain. Although overall use of CAM among adults has remained relatively stable since 2002 (the last time NHIS included a CAM section), the use of some specific CAM therapies has varied substantially; for example, deep breathing, meditation, massage therapy, and yoga have all shown significant increases. The 2007 NHIS was the first to ask about CAM use by children. The NHIS also reports on characteristics of CAM users, such as gender, age, education, geographic region, poverty status, and health indicators. The 2007 NHIS provides the most current, comprehensive, and reliable source of information on Americans' use of CAM. These statistics confirm that CAM practices are a frequently used component of American's health care regimens, and reinforce the need for rigorous research to study the safety and effectiveness of these therapies. The data also point out the need for patients and health care providers to openly discuss CAM use to ensure safe and coordinated care. Future analyses of these data may help explain some of the observed variation in the use of individual CAM therapies and provide greater insights into CAM use patterns among Americans.

- Barnes PM, et al. *Natl Health Stat Report* 2008;(12):1-23. PMID: 19361005.
- For more information, see <http://www.cdc.gov/nchs/data/nhsr/nhsr012.pdf>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NCCAM, CDC)

Half of Surveyed Physicians Use Placebo Treatments for Patients: Treating patients with placebos has a long, complicated, and often controversial history. Nonetheless, little actually is known about U.S. physicians' current attitudes toward and use of placebo treatments. A national survey funded in part by NIH looked at placebo-prescribing practices among 679 internists and rheumatologists—specialties that commonly treat patients with debilitating chronic conditions. The survey found that about half of the physician respondents prescribed placebo treatments on a regular basis. Most (62%) said they think the practice is ethical. Among physicians who prescribed placebos, few said they used inert treatments such as saline injections or sugar pills; they were more likely to recommend over-the-counter analgesics (41%) or vitamins (38%), and some used antibiotics (13%) or sedatives (13%) as placebos. The survey also found that the physicians who used placebos rarely described them as such to patients. Instead, physicians most commonly described the treatments as medicine that typically is not used for the patient's condition but that might be beneficial. The survey provides insights into the complex relationship between placebo use and physicians' traditional role in promoting positive expectations in their patients. It also raises concerns about the use of "active" placebos, particularly antibiotics and sedatives, when they are not medically indicated. Prescribing placebo treatments remains an appropriate topic for ethical and policy debates.

- Tilburt JC, et al. *BMJ* 2008 Oct 23;337:a1938. PMID: 18948346. PMCID: PMC2572204.
- For more information, see <http://nccam.nih.gov/research/results/spotlight/102408.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NCCAM)

Research Resources, Infrastructure and Technology

Unique Compounds Added to Chemical Libraries: Potent, drug-like molecules that selectively bind to the kappa opioid receptor have potential utility in the treatment of drug addiction, depression, psychosis and dementia, pain, and even HIV infection. Well more than 100 unique, new molecules constructed independently by two NIH-supported groups have been found to provide entirely new classes of kappa opioid binders. These molecules are potent and display a diversity of pharmacological activities that are under intensive active investigation.

Molecular Biology and Basic Research

- Beeler AB, et al. *J Comb Chem* 2005;7(5):673-81. PMID: 16153061.
- For more information, see http://www.cml.d.ku.edu/sbc_photos.shtml
- For more information, see <http://pdsp.med.unc.edu/indexR.html>
- This example also appears in Chapter 3: *Technology Development*
- (E) (NIGMS) (GPRA)

National Centers for Biomedical Computing: There are seven NIH Roadmap National Centers for Biomedical Computing (NCBC). Funded as cooperative agreements, these centers collectively cover broad areas of neuroinformatics, functional genomics, image post processing, multiscale modeling, cellular pathways, semantic data integration and ontologies, information networks, cellular networks and pathways, clinical informatics, disease-gene-environment analysis, and clinical decisions support.

- For more information, see <http://ncbcs.org/>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Technology Development*
- (E) (NIGMS, Common Fund - all ICs participate)

Influenza Virus Resources: NIH maintains the Influenza Virus Resource, a database of influenza virus sequences that enables researchers around the world to compare different virus strains, identify genetic factors that determine the virulence of virus strains, and look for new therapeutic, diagnostic, and vaccine targets. The resource was developed using publicly accessible data from laboratories worldwide in addition to targeted sequencing programs such as NIH's Influenza Genome Sequencing Project. Updated daily, this comprehensive sequence resource includes more than 90,000 influenza sequences and more than 2,000 complete genomes. In the spring of 2009, with the rapid emergence of the 2009 H1N1 pandemic, the database received more than 2,200 influenza sequences from publicly accessible databases and included sequences from CDC and labs from 35 countries. By the end of 2009, nearly 10,000 H1N1 sequences were in the database. The combination of extensive sequence data and advanced analytic tools provided researchers worldwide immediate access for investigating the rapid spread of this flu and developing vaccines for combating it. Other influenza virus information resources also were developed in response to 2009 H1N1. To facilitate access to the scientific literature, a pre-formulated search for 2009 H1N1 papers was added to PubMed. A 2009 H1N1 Flu page with comprehensive information on Federal response, international resources, transmission, prevention, treatment, genetic makeup, and veterinary resources was added to Enviro-Health Links, which provides links to toxicology and environmental health topics of recent special interest, including information in Spanish. For the general public, patients, family members, and caregivers, a health topic on 2009 H1N1 flu, in Spanish and English, was added to the MedlinePlus consumer health resource.

- Bao Y, et al. *J Virol* 2008;82(2):596-601. PMID: 17942553. PMCID: PMC2224563.
- For more information, see <http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html>
- For more information, see <http://www.pubmed.gov>
- For more information, see <http://sis.nlm.nih.gov/enviro/swineflu.html>
- For more information, see <http://www.nlm.nih.gov/medlineplus/h1n1fluswineflu.html>
- For more information, see <http://www.nlm.nih.gov/medlineplus/spanish/h1n1fluswineflu.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (NLM)

Centers of Excellence for Influenza Research and Surveillance: NIH established the Centers of Excellence for Influenza Research and Surveillance (CEIRS) program in March 2007 to continue and expand its animal influenza surveillance program internationally and domestically, and to focus on several high-priority areas in influenza research.

The program provides the government with information and public health tools and strategies to control and lessen the impact of epidemic influenza and the increasing threat of pandemic influenza. CEIRS activities lay the groundwork for the development of new and improved control measures for emerging and reemerging influenza viruses. Such measures include determining the prevalence of avian influenza viruses in animals in close contact with humans; understanding how influenza viruses evolve, adapt, and transmit; and identifying immunological factors that determine disease outcome. Each CEIRS site focuses on either (1) animal influenza surveillance for the rapid detection and characterization of influenza viruses with pandemic potential, or (2) pathogenesis and host response research to enhance understanding of the molecular, ecological, and/or environmental factors that influence pathogenesis, transmission, and evolution of influenza viruses; and to characterize the protective immune response. Currently, the CEIRS are responding to the 2009 H1N1 influenza outbreak by conducting research on pathogenicity and transmission of H1N1 and studying immune response to this novel influenza strain.

- For more information, see <http://www3.niaid.nih.gov/topics/Flu/default.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIAID)

Collective Intelligence for Knowledge Discovery: NIH has started a new NIH initiative in collective intelligence. The goal is to create deep repositories of knowledge backed by controlled vocabularies or ontologies, and to create or enhance semantically interoperable applications capable of discovering knowledge hidden within these repositories. Current applications such as the Human Salivary Proteome Annotation System, the Common Assay Reporting System, and the caBIG Protocol Lifecycle Tracking Tool are among the initial steps of a knowledge infrastructure. These applications harvest the collective knowledge of targeted scientific communities to store protocols, data, and results. Other tools developed for this initiative (e.g., the context-sensitive text mining system for identification of high-risk, high-reward research) use statistical natural language processing to discover new knowledge, such as, whether in peer review, an application for funding was considered high-risk and high-reward. Additional pilot studies are evaluating computational linguistics and knowledge management tools for biomedical and clinical informatics, portfolio analysis, systems biology, proteomics, genomics, and knowledge representation paradigms. The collective-intelligence initiative will lead to a knowledge infrastructure that can shift the paradigms of data re-use and knowledge discovery dramatically.

- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (CIT, CC, NCI, NHGRI, NIDCR, NIMH, OD)

NIGMS/NCI Collaborative Access Team (GM/CA-CAT): Structural biology is a field in which scientists learn about molecules by determining their 3-D structures in atom-by-atom detail. Large user facilities called synchrotrons allow researchers to use X-rays to determine molecular structures more easily, quickly, and cheaply than ever before. Two NIH institutes (NIGMS and NCI) funded the development of a new experimental station at the Advanced Photon Source at Argonne National Laboratory. The new station includes three X-ray beamlines for use by scientists from across the United States to determine the detailed, three-dimensional structures of molecules. Two of these beamlines provide world-leading capabilities for X-ray diffraction data from very small protein crystals only a few microns in dimension. This research capability is important to understand basic biological processes and for drug design. The facility now is in full operation.

- For more information, see <http://www.gmca.anl.gov>
- This example also appears in Chapter 3: *Technology Development*
- (E) (NIGMS, NCI)

Molecular Biology and Basic Research

Collaborations Between Minority-Serving Institutions and Cancer Centers: The Minority Institution (MI)/Cancer Center (CC) Partnership (MI/CCP) is a flagship program that has been instrumental in establishing strong collaborations between minority-serving institutions (MSIs) and CCs. MI/CCP has fostered strong cancer research partnerships throughout the United States. This program established new cancer research curricula, recruited new faculty, increased awareness about health care disparities and cultural sensitivities, and developed programs and outreach efforts in educating underserved communities. The MI/CCP has provided research education and training to individuals at all levels including postdoctoral fellows, medical students, graduate students, students at master's level, and baccalaureate and high school students. Establishing new collaborations and partnerships in communities has been a hallmark of this program, culminating in increases in numbers of awarded grant applications and numbers of manuscripts, oral presentations, and poster presentations at both regional and national levels. Many research advances are emerging from the Partnership. For example, through the Morehouse School of Medicine and University of Alabama Partnership, researchers have identified a possible genetic cause for increased risk for a more advanced form of colorectal cancer in blacks that leads to shorter survival. Understanding the relationship between molecular defects and differences in colorectal cancer incidence, aggressiveness, and clinical outcomes is important in individualizing the treatment and in eliminating racial disparities.

- For more information, see <http://crchd.cancer.gov/research/miccp-overview.html>
- For more information, see <http://clincancerres.aacrjournals.org/cgi/content/full/15/7/2406>
- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
- (E) (NCI)

Biomedical Technology Research Centers (BTRCs): The BTRCs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Centers and through intensive collaborations with other leading laboratories. The BTRCs are used annually by nearly 5,000 scientists from across the United States and beyond, representing more than \$700 million of NIH funding from 22 ICs. As an example, optical technologies enable researchers to:

- Harness the power of light to "see" biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

- For more information, see http://www.ncrr.nih.gov/biomedical_technology
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
- (E) (NCRR)

Extramural Construction Program Expands Research Capacity: The American Recovery and Reinvestment Act (ARRA) provided \$1 billion to NIH for the Extramural Construction program. The program will build capacity to conduct biomedical and behavioral research by supporting the costs of improving non-Federal basic research, clinical research, and animal facilities to meet the research, research training, or research support needs of institutions. One component of the program, the Extramural Research Improvement Program, awards grants to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities for biomedical and behavioral research. Another component of the program, the Core Facility Renovation, Repair, and Improvement activity, awards

grants to public and nonprofit private entities to renovate, repair, or improve core facilities. A core facility is a centralized shared resource that provides access to instruments or technologies or services, as well as expert consultation to investigators supported by the core. Institutions apply for construction grants by submitting applications, which are selected using NIH's standard, competitive, peer-reviewed process. Funding decisions are based on the scientific and technical merit of the application as determined by first and second level of peer review, the availability of funds, the relevance of the application to NIH program priorities, the national geographic distribution of awards, and the priorities specified in the ARRA, such as energy efficiency and job creation. The objective of the ARRA Extramural Construction program aligns with the objective of the existing Research Facilities Improvement Program, which is also administered by NIH.

- For more information, see <http://www.ncrr.nih.gov/recovery/construction>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
- (E) (NCRR) (ARRA)

Shared Instrumentation Grant and High-End Instrumentation Programs: The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the \$100,000-\$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the \$750,000-\$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located at core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2008, the SIG program funded a total of 82 grants for \$30,623,406; the HEI funded a total of 20 awards for \$33,309,434. In FY 2009, NIH received \$300 million in ARRA funding to provide shared instrumentation to extramural researchers through the SIG and HEI programs. To best serve the needs of NIH-supported investigators, the range of HEI awards funded by ARRA was expanded and now is \$600,000 to \$8 million.

- For more information, see <http://www.ncrr.nih.gov/btinstruments>
- For more information, see <http://www.ncrr.nih.gov/recovery>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
- (E) (NCRR) (ARRA)

Stimulating Innovation

The NIH Director's New Innovator Award Program: The NIH Director's New Innovator Award addresses two important goals: stimulating highly innovative research and supporting promising new investigators. The award supports new investigators who propose exceptionally innovative research ideas but lack the preliminary data required to fare well in the traditional NIH peer review system. Award recipients have discovered important insights about Parkinson's genes and manganese poisoning, and protein folding and diabetes.

- *Link between Parkinson's disease genes and manganese poisoning:* Manganese poisoning, prevalent in such occupations as mining, welding, and steel manufacturing, damages the central nervous system, producing motor and dementia symptoms that resemble Parkinson's disease. One New Innovator recipient's team found a genetic interaction between two Parkinson's disease genes (alpha-synuclein and PARK9) and determined that the PARK9 protein can protect cells from manganese poisoning. Yeast cells contain a gene nearly identical to PARK9, and the team showed that expression of this gene protects yeast cells from the toxicity caused by alpha-synuclein. The team

Molecular Biology and Basic Research

found that the PARK9 gene in yeast also codes for a metal transporter protein. Cells with a defect in this gene, coupled with manganese exposure, did not grow well. These results may explain the origin of at least one type of Parkinson's disease.

- *Protein folding and diabetes:* Individual protein molecules do not always fold correctly into their normal shapes. A compartment within cells called the endoplasmic reticulum (ER) acts as a protein-folding factory for secreted proteins such as insulin. Another New Innovator recipient hypothesized that unrelenting insulin production can overtax the ER, leading to the condition of "ER stress." This triggers a chain of events that leads the insulin-making beta cells to commit suicide. This new knowledge could be used to identify new molecules as targets for the development of what may prove to be totally new types of drugs to fight diabetes.
 - Merksamer PI, et al. *Cell* 2008;135(5):933-47. Comment in *Cell* 2008;135(5):78-9. PMID: 19026441. PMCID: PMC2739138.
 - For more information, see <http://www.nature.com/ng/journal/v41/n3/abs/ng.300.html>
 - (E) (NIGMS)

The NIH Director's Pioneer Award: The NIH Director's Pioneer Award Program is designed to support highly innovative approaches to addressing major challenges in biomedical and behavioral research. By supporting scientists of exceptional creativity who propose pioneering and possibly transformative approaches, NIH intends to encourage novel investigator-initiated research that would have an unusually high scientific impact. Already, several recipients of the Award have discovered important insights, e.g., in Parkinson's disease, therapies for neurodegenerative diseases, and targets for cancer therapies.

- *Parkinson's disease and possible treatments:* Using an approach dubbed "optigenetics," one Pioneer Award recipient found that stimulating axons that connect directly to the subthalamic nucleus from areas closer to the surface of the brain in rodents has the biggest effect on treating "parkinsonism." This insight could lead to the development of less invasive treatments for patients with Parkinson's disease.
- *Personalized therapies for neurodegenerative diseases using RNA to reprogram cells:* Another recipient has shown that by flooding a nerve cell with a specific type of messenger RNA from another cell type, researchers could reprogram the nerve cell. The approach, called Transcriptome Induced Phenotype Remodeling, suggests a new type of cell-based therapy for neurodegenerative and other diseases.
- *Research in mice and human cells suggests new cancer therapeutic targets:* Another Pioneer Award study showed that a single extra copy of a particular gene on chromosome 21 is sufficient to significantly suppress angiogenesis (growth of new blood vessels) and tumor growth in mice, as well as angiogenesis in human cells. The study also showed that the protein expressed by the gene under study, DSCR1, is elevated in tissues from people with Down syndrome and in a mouse model of the disease. Given that the incidence of many cancers is significantly reduced in individuals with Down syndrome, this finding suggests a new target for cancer therapies.
 - Gradinaru V, et al. *Science* 2009;324(5925):354-359. PMID: 19299587.
 - Sul JY, et al. *Proc Natl Acad Sci U S A* 2009;106(18):7624-9. PMID: 19380745. PMCID: PMC2670883.
 - For more information, see <http://www.nature.com/nature/journal/vaop/ncurrent/full/nature08062.html>
 - (E) (NIGMS)

Building Interdisciplinary Research Teams (BIRT) Awards: The scale and complexity of biomedical research demands that scientists move beyond the confines of their individual disciplines and explore new organizational models for team science. Integrating different disciplines holds the promise of opening scientific avenues of inquiry and, in the process, potentially forms new disciplines for addressing increasingly complex questions. The BIRT award was created by NIH to promote interdisciplinary research by supplementing collaborations with high innovation and potentially high impact in general areas of arthritis, musculoskeletal, and skin biology and diseases. In 2008, 11 grants were awarded for

the following areas of collaboration: developmental biology—systems biology, soft tissue biology—imaging technologies, tissue engineering—immunology, and tissue engineering—developmental biology.

- For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2008/birt.asp
- For more information, see http://www.niams.nih.gov/Funding/Funding_Opportunities/Supported_Scientific_Areas/Musculoskeletal_Diseases/birt_faq.asp
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-08-001.html>
- This example also appears in Chapter 3: *Technology Development*
- (E) (NIAMS)

Cancer Health Disparities Research Programs and Initiatives: NIH has expanded research on the basic biologic factors of cancer disparities to provide a foundation for minimizing risk, identifying targets, developing preventive and therapeutic interventions, and understanding how genetic susceptibility may be influenced by social, economic, race/ethnicity, and geographic factors. Thus, the research programs involve multidisciplinary teams, which contribute to understanding the etiology of cancer and build prevention and intervention evidence-based models to eliminate cancer disparities. Several programs at NIH address disparities along the cancer continuum from prevention to survival.

- The trans-disciplinary Geographic Management Program (GMaP) pilot initiative builds regional networks to support research, training, and infrastructure to develop state-of-the-art networks/centers to ensure a continuous supply of high-quality human biospecimens from multi-ethnic communities.
 - The Community Networks Program engages communities experiencing cancer disparities to design, test, and evaluate evidence-based strategies to address critical needs, such as access to screening, mentoring, and training; policy development; and community outreach and education.
 - The Patient Navigation Research Program builds partnerships to ensure that racial/ethnic minorities and underserved populations with abnormal cancer screening results receive appropriate care.
 - The Community Clinical Oncology Program is a network for conducting cancer prevention and treatment clinical trials by connecting academic centers with community physicians.
 - The NIH Centers for Population Health and Health Disparities catalyze transdisciplinary research to improve the understanding of complex interactions of biological, social, cultural, environmental, and behavioral factors that contribute to health inequities, and to develop and implement novel intervention strategies that are multilevel and multifactorial.
 - The Tobacco Research Network on Disparities' mission is to understand and address tobacco-related disparities by advancing the science, translating that scientific knowledge into practice, and informing public policy.
 - The Centers of Excellence in Cancer Communication Research continue to use best practices in communication science to extend the reach of biomedical benefits equitably throughout the population.
- For more information, see <http://crchd.cancer.gov/>
 - For more information, see <http://crchd.cancer.gov/cnp/background.html>
 - For more information, see <http://crchd.cancer.gov/pnp/pnpr-index.html>
 - For more information, see <http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html>
 - This example also appears in Chapter 2: *Cancer*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
 - (E) (NCI)

Cooperation in Space-Related Health Research: In FY 2009, NIH and the National Aeronautics and Space Administration (NASA) issued a funding opportunity announcement to support biomedical experiments that astronauts could perform on the International Space Station (ISS). The ISS provides a special microgravity and radiological environment that Earth-based laboratories cannot replicate. Congress, recognizing the immense promise the facility holds for American-led science and technology efforts, opened the U.S. portion of the ISS to other Federal agencies and

Molecular Biology and Basic Research

university and private sector researchers when it designated the U.S. resources as a National Laboratory in 2005. Recently published ISS experiments from investigators supported by NIH and NASA have offered new insights into how bacteria cause infectious disease. The FY 2009 solicitation is the next step in a partnership to apply the National Laboratory to research that complements NASA's space exploration efforts. The program encourages a new cadre of health researchers from a variety of disciplines to incorporate the space environment into their experiments, and will support them as they prepare their experiments for launch and analyze their data following a mission. Applications particularly are encouraged from researchers who are interested in molecular or cellular biology, biomaterials, or telemedicine. NIH expects to fund applications in FY 2010, FY 2011, and FY 2012, and to send experiments into space by 2011.

- Wilson JW, et al. *Proc Natl Acad Sci U S A* 2007;104(41):16299-304. PMID: 17901201. PMCID: PMC2042201.
- For more information, see http://www.niams.nih.gov/News_and_Events/NIH_NASA_Activities/default.asp
- This example also appears in Chapter 3: *Technology Development*
- (E) (NIAMS, NCI, NCRR, NHLBI, NIA, NIAAA, NIBIB, NICHD, NINDS)

- ³¹ Liu GY, et al. *J Exp Med* 2005;202(2):209-15. PMID: 16009720. PMCID: PMC2213009.
- ³² For more information, see <http://www.nih.gov/news/health/feb2008/nigms-14.htm>.
- ³³ Liu CI, et al. *Science* 2008;319(5868):1391-4. PMID: 18276850. PMCID: PMC2747771.
- ³⁴ Song Y, et al. *J Med Chem* 2009;52:3869-80. PMID: 19456099. PMCID: PMC2753857.
- ³⁵ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-040.html>.
- ³⁶ Ganeshan K, et al. *J Allergy Clin Immunol* 2009;123(1):231-238.e4. PMID: 19022495. PMCID: PMC2787105.
- ³⁷ Kawasaki Y, et al. *Nat Med* 2008;14:331-6. PMID: 18264108. PMCID: PMC2279180.
- ³⁸ Li J, Wang C-Y. *Nat Cell Biol* 2008;10(2):160-9. PMID: 18193033.
- ³⁹ Nesti LJ, et al. *J Bone Joint Surg Am* 2008;90(11):2390-8. PMID: 18978407. PMCID: PMC2657299.
- ⁴⁰ Gowher H, et al. *Genes Dev* 2008;22:2075-84. PMID: 18676812. PMCID: PMC2492749.
- ⁴¹ For more information, see <http://nihroadmap.nih.gov/epigenomics/fundedresearch.asp>.
- ⁴² Denny P, et al. *J Proteome Res* 2008;7(5):1994-2006. PMID: 18361515. PMCID: PMC2839126.
- ⁴³ For more information, see http://www.nih.gov/news/research_matters/february2009/02232009cancer.htm.
- ⁴⁴ Shukla AK, et al. *Mol Pharmacol* 2008;73(5):1333-8. PMID: 18239031.
- ⁴⁵ Rasmussen SG, et al. *Nature* 2007;450:383-7. PMID: 17952055.
- ⁴⁶ Service RF. *Science* 2009;325(5945):1200. PMID: 19729635.
- ⁴⁷ Mazumdar V, et al. *J Bacteriol* 2008;191(1):74-90. PMID: 18931137. PMCID: PMC2612419.

Clinical and Translational Research

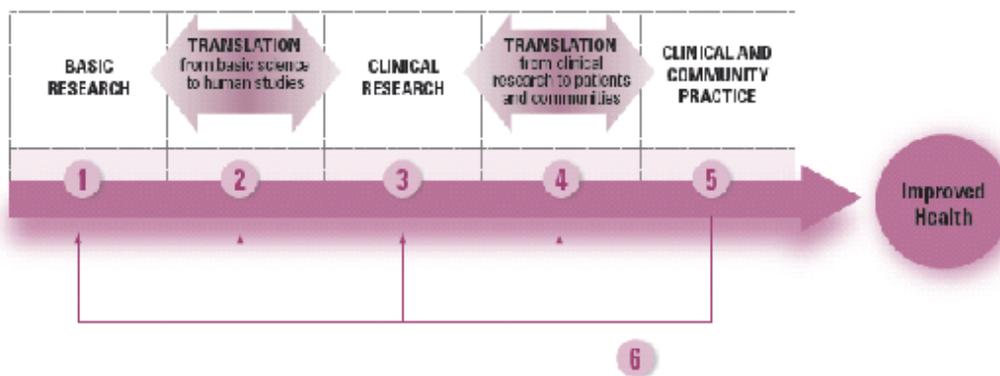
The obesity epidemic combined with an aging population has made diabetes the most common cause of kidney failure, nontraumatic lower limb amputation, and new cases of blindness among working-age Americans. Diabetes also is a leading cause of heart disease and stroke. Nearly 11 percent of American adults 20 years and older have diabetes and 57 million have pre-diabetes—elevated blood sugar levels not yet in the diabetic range. African Americans, Hispanic/Latino Americans, American Indians, Asian Americans, and Pacific Islanders are at particularly high risk.⁴⁸ Globally, more than 180 million people have diabetes, and the number is likely to more than double by 2030.⁴⁹

The landmark NIH-supported Diabetes Prevention Program (DPP) clinical trial sought ways to prevent type 2 diabetes and found that a lifestyle intervention—reduced dietary fat and calories, moderate exercise, and a goal of a 7 percent reduction in body weight—lowered the risk of developing type 2 diabetes by 58 percent. Study participants receiving the drug metformin along with standard medical advice about diet and exercise had a 31 percent lower risk than those receiving standard medical advice alone. The interventions worked in all ethnic and racial groups studied, in both men and women, and in women with a history of gestational diabetes.^{50,51} The DPP Outcomes Study continues to follow most of the participants to evaluate the lasting benefits of the interventions. The critical challenge today is to move this proven program into widespread use. NIH is supporting translational research to find better methods for identifying people with pre-diabetes and to develop cost-effective ways of implementing the DPP-based lifestyle intervention. One successful program is delivering a lifestyle intervention based on the DPP in a group setting at YMCAs.⁵²

Introduction

As the steward of medical and behavioral research for the Nation, NIH is supporting scientific research in pursuit of fundamental knowledge about the nature and behavior of living systems and the mechanisms of disease. Achieving this mission requires a research continuum from basic discovery to accelerated translation of biomedical discoveries into clinical and community practice, with feedback loops at every step (Figure 3-1). In this report, clinical and translational research are considered together because the two areas overlap, with translational efforts often focusing on dismantling barriers that slow the progress of clinical research or impede the adoption of new and effective interventions.

Figure 3-1. NIH Supports the Full Continuum of Biomedical Research



1. The research continuum begins with **basic research**—the study of the fundamental mechanisms of disease and behavior. Basic research is a major force for progress in the biomedical and behavioral sciences and can lead to insights essential to understanding basic human biology and behavior in both normal and diseased states. Basic research is thus a

critical component of the Nation's public investment in research and a central feature of NIH's research program. (Also see the section on *Molecular Biology and Basic Sciences* in Chapter 3.)

2. NIH is a key supporter of **early (or preclinical) translational research**—studies that serve as a bridge between basic science and human medicine. The early translational stage applies fundamental laboratory discoveries to the preclinical development of studies in humans. Such early translational investigations often are carried out using animal models, cultures, samples of human or animal cells, or a variety of experimental systems such as computer-assisted modeling of disease progression and drug therapy.

3. **Clinical research** is patient-oriented research that is conducted with human subjects (that is, studies that involve direct interaction between investigators and human subjects or the use of material of human origin, such as tissues, specimens, and data that retain information that would allow the investigator to readily ascertain the identity of the subject). Clinical research includes clinical trials, behavioral and observational studies (also see the section on *Epidemiological and Longitudinal Studies* in Chapter 3), outcomes and health services research, as well as the testing and refinement of new technologies. Investigations that use only anonymous specimens or other "de-identified" data from human subjects, however, are excluded from the umbrella of clinical research. Such studies would likely fall into the categories of basic or early translational research.

Clinical trials, a crucial subset of clinical research, are the best method of determining whether interventions are safe and effective in people and assessing side effects or other complications. Trials are designed to answer specific research questions about a biomedical or behavioral intervention. For example, treatment trials might test experimental drugs or devices, new combinations of drugs, innovative approaches to surgery or radiation therapy, or behavioral interventions such as exercise training or medication adherence. Prevention trials test the effectiveness of approaches to prevent diseases or other adverse health conditions or to keep them from recurring. Comparative effectiveness research entails real-world comparisons of known interventions. (Also see the section on *Chronic Diseases and Organ Systems* in Chapter 2.) Screening and diagnostic trials are conducted to find better ways to detect or diagnose diseases or conditions. Finally, quality-of-life trials (or supportive care trials) explore ways to improve people's comfort and ability to continue the activities of daily life even as they deal with chronic illnesses or approach the end of life.

NIH also funds the development of consortia, cooperative study groups, and networks that enable a single institution or researcher to combine resources and knowledge with others. Consortia are particularly useful for studying rare diseases, and they allow clinical trials to more rapidly recruit sufficient numbers of participants to speed the delivery of new treatments to patients. The matrix of research support arising from such partnerships creates a whole that is much greater than the sum of the separate programs.

4. A key goal of NIH research efforts is to bring effective prevention and treatment strategies more quickly into practice to improve population health, both domestically and globally. The **late (or postclinical) translational stage** takes results from studies in humans and applies them to research on enhancing the adoption of best practices in the community. NIH investigates strategies for disseminating information to providers and the public about the latest research findings and encourages health care providers to participate in clinical research.

NIH collaborative activities in translational research take place within most ICs and almost every other HHS agency. The collaborations include working groups and committees such as the Biomedical Imaging in Oncology Forum, the Joint Working Group on Telehealth, and the Health Literacy Workgroup; a wide range of translational research such as projects on vaccine safety, child abuse and neglect, diabetes prevention, and health disparities; and database development and management such as the Stem Cell Therapeutics Outcomes Database.

The Federal government plays a critical role in focusing on gaps in clinical and translational research that would otherwise remain unaddressed by other entities (e.g., pharmaceutical companies, nonprofit organizations). Specifically, NIH supports clinical and translational studies unlikely to garner substantial investment by other sources because of insufficient financial

Clinical and Translational Research

incentives—for example, studies that address rare diseases, are considered high risk, or are based on lifestyle alterations or behavioral changes rather than drugs or devices.

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5. Important new discoveries can improve population health and reduce disease burdens only if they are integrated into care. Therefore, NIH is taking a lead in applying evidence-based methods to inform the public and health care practitioners about research results and facilitate the implementation of safe and effective interventions in the **community and the clinic**.

6. Although sometimes referred to as bench-to-bedside research, translational research is really a two-way street, with each stage informing and influencing the others. Basic research scientists provide clinicians with new tools for use with patients, and clinical researchers make new observations about the nature and progression of disease that often feed back to stimulate new basic investigations. Research on new outreach approaches and the comparative effectiveness of prevention and treatment strategies also are important activities to ensure the feasibility of such strategies and to inform the development of future interventions.

Every NIH component supports clinical and translational research. NIH's ICs oversee a broad portfolio of clinical and translational research that encompasses intramural and extramural programs. (Also see the section on *Extramural and Intramural Research Programs* in Chapter 1.) NIH intramural research laboratories are conducting cutting-edge biomedical research in a wide range of fields at its main campus in Bethesda, Maryland, and several satellite locations. Central to the intramural program is the NIH Clinical Center, the Nation's largest hospital devoted entirely to clinical research. The Clinical Center serves more than 7,000 inpatients and more than 100,000 outpatients annually. To receive medical care at the Clinical Center, individuals need to meet the eligibility criteria for and agree to participate in a research trial.

The NIH extramural program, in addition to supporting both investigator- and NIH-initiated clinical and translational research, builds collaborations among institutions, industry (e.g., pharmaceutical companies), and local communities; sets up innovative centers of clinical and translational research; undertakes animal and other preclinical studies; and develops new resources and tools for research. Training and career development initiatives help ensure that enough highly trained and diverse groups of basic, clinical, and translational scientists are available with appropriate research knowledge to carry out the country's biomedical and behavioral research agendas. (Also see the section on *Research Training and Career Development* in Chapter 3.)

NIH Roadmap initiatives are helping to accelerate and strengthen movement along the research continuum by ensuring that basic discoveries are translated into interventions to improve health. These initiatives are supporting the development of research networks, outcome assessment tools, core services and resources, policy enhancement and harmonization, and a Clinical and Translational Science Award (CTSA) program. Thanks to such programs, the clinical research enterprise is being transformed to speed the progression of new discoveries from bench to bedside and community.

Catalogs of Clinical and Translational Research Activities

In response to the mandate under SEC. 403 (a)(4)(C)(v) of the Public Health Service Act to provide a catalog of clinical trials, provided here is a live link to the service called [ClinicalTrials.gov](https://clinicaltrials.gov), a registry of federally and privately supported clinical trials conducted in the United States and around the world. [ClinicalTrials.gov](https://clinicaltrials.gov) provides information about a trial's purpose, who may participate, locations, and phone numbers for more details.

In response to the mandate under SEC. 403 (a)(4)(C)(v) of the Public Health Service Act to provide a breakdown of study populations by demographic variable, provided here is a link to NIH's Biennial Report on its tracking efforts regarding study demographics: *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*. (Please also see Appendix D, which provides an excerpt of that report.)

In response to the mandate under SEC. 403 (a)(4)(C)(vi) for a catalog of translational research activities with other agencies of the Public Health Service, included here is a live link to the Catalog of Trans-HHS Translational Research Activities FYs 2007 & 2008. This is an excerpt from another congressionally mandated report, the Annual Report to the Secretary, HHS, on *NIH Collaboration with Other HHS Agencies*.

Summary of NIH Activities

NIH nurtures strategies that bring basic research discoveries to human studies, optimize the conduct of clinical research, and facilitate the transfer of new knowledge gained through research into clinical practice, thereby aligning and reinforcing the entire research continuum. The following summary delineates some specific strategies employed by the ICs to propel research along the research continuum and highlight a few examples from NIH's robust portfolio of clinical and translational research.

Preclinical Research: Translating Basic Science Discoveries to Human Studies

Before investigators can conduct human studies, extensive basic and preclinical research must be done and a supportive infrastructure must be in place. NIH equips translational scientists with research tools, enhances opportunities for collaborative research, and provides resources for developing and testing new drugs before progressing to human studies. The result has been the creation of exciting possibilities in terms of new investigational drugs and devices ready for safety and efficacy testing in humans, including:

- In the past 2 years, NIH-funded scientists have published several papers on compounds that improve muscle function and endurance in animals. They hope that this new knowledge can be applied to improve treatments for certain muscle disorders, frailty, obesity, and other conditions.
- Laboratories have been established to screen promising compounds for treating alcohol dependence in animal models, thereby enabling faster determination of those that merit advancement to large, multisite studies.
- NIH-supported investigations have successfully decoded the genome of the parasite that causes relapsing malaria and determined that the anti-malarial drug chloroquine may once again be used to prevent malaria in African children.

Research Tools and Resources

Preclinical research results derived from animal models are an essential element in the translational process of determining whether a basic science discovery is a potential therapeutic approach worthy of future development. Scientists who work with animal models can look forward to a new online tool to increase research efficiency, improve collaboration, and ultimately help bridge the gap between basic science and human medicine. With funding from NIH, the Linking Animal Models to Human Disease Initiative will integrate data and information about animal models and make them available to health researchers to help them identify the most useful animal models for their research.

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Nonhuman primates are critical resources for translational research because of their close physiological similarities to humans. The NIH-supported National Primate Research Centers (NPRCs) and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using nonhuman primates. In FY 2008, more than 2,000 investigators used nonhuman primates from the NPRCs. One highlight

Clinical and Translational Research

of research conducted at a NPRC was the development and characterization of the first nonhuman primate model of a neurodegenerative condition—Huntington’s disease.⁵³ This new model will make it possible to study a wide range of therapeutic strategies to help people who have the devastating fatal disease.

Among the many research tools that NIH provides to promote early translational studies are biosample and data repositories. Central repositories allow additional studies on human tissue samples and data collected during clinical research, enhancing the value of each study and making optimal use of samples and data. The use of repositories also ensures that samples are stored under uniform conditions and are readily accessible to the scientific community. Samples and data are labeled with codes to keep the study participants’ information confidential. Although numerous regulations and policies apply to research on human samples and data, currently no comprehensive Federal policy covers the full spectrum of activities involved with collection, storage, sharing, distribution, and use of human specimens or data for research. To address this gap, NIH is developing draft guidelines for human specimen and data collections owned or supported by NIH. The guidelines cover ethical and regulatory issues and provide vital information about managing, accessing, sharing, and using the stored specimens and data. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.)

A recent Alzheimer’s Disease Neuroimaging Initiative study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer’s disease and established a method and standard for testing for these biomarkers.

Researchers from several ICs are identifying, developing, and validating new biomarkers—physical, functional, or biochemical indicators of physiologic or disease processes. Biomarkers play important roles in the diagnosis of disease, identification of patient populations that could benefit from particular therapies, and the monitoring of treatment effectiveness. The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is a noteworthy example of an innovative public-private partnership for examining the utility of magnetic resonance imaging, positron emission tomography, or other methods to identify biomarkers that will enable clinicians and investigators to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer’s disease. ADNI has provided evidence to support development of a number of tools and methods now in use in the United States and abroad. A recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer’s disease and established a method and standard for testing for these biomarkers. (Also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2 and the section on *Alzheimer’s Disease Centers* in Chapter 4.)

Collaborative Science

Oftentimes, translational research can be streamlined or conducted more economically when scientists within NIH, private industry, academia, private practices, or other institutions work in partnership to complement each other’s strengths and share costly resources or infrastructure. As its name implies, the NIH Bench-to-Bedside Program spans the research continuum with its focus on collaboration between basic and clinical investigators working to translate fundamental scientific discoveries into diagnostic and therapeutic applications at the bedside. This program also bridges the intramural and extramural research communities and fosters interagency collaborations.

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In addition, through the Strategic Partnering to Evaluate Cancer Signatures initiative, NIH is bringing together interdisciplinary teams at various institutions to discover, develop, and test biomarkers that can be used to characterize an individual’s disease or tumor. Armed with such information, clinicians can tailor a patient’s cancer treatment based on

molecular characteristics of the patient and tumor. Several published studies have already demonstrated the usefulness of this personalized approach to cancer therapy. (Also see the section on *Cancer* in Chapter 2.)

Resources for Developing and Testing Investigational Drugs

NIH helps bridge the gap between drug discovery and clinical testing of promising new agents. Translating promising compounds into drugs for human use is a task that requires very specific, interrelated activities. NIH provides state-of-the-science preclinical drug development resources. Specifically, NIH helps investigators by providing large quantities of promising investigational drugs to test in clinical trials, and clarifying regulatory issues so that FDA requirements are likely to be satisfied when the new investigational drugs are ready for testing in the clinic. For example, the NCI Experimental Therapeutics program (NExT) is an integrated drug discovery and development effort that concentrates research into a single robust pipeline that starts with discovery of promising compounds and follows a series of progressive steps leading to early-phase clinical studies. The NExT program aims to produce a diverse portfolio of assays and imaging tools that are available in the public domain. It is anticipated that this investment will reap many benefits by making a library of new molecular tools available to all researchers in the cancer research community for use in assessing new targeted drugs and diagnostics. (Also see the section on *Cancer* in Chapter 2.)

A menu of preclinical drug development contract resources is offered through one of NIH's Roadmap initiatives, the Rapid Access to Intervention Development (RAID) program. The NIH-RAID program makes accessible, on a competitive basis and at no cost to investigators, certain critical resources needed to develop new therapeutic agents, including not only laboratory services but also expertise in the regulatory process. The program directly addresses roadblocks to moving research findings from bench to bedside. Among the projects approved are potential therapies for hepatic fibrosis, sickle cell anemia, drug abuse, and Crohn's disease.

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To move basic research on Alzheimer's disease and associated disorders into the realm of translational research and drug testing in clinical trials, NIH is providing resources for preclinical development of investigational drugs and toxicology studies for academic and small business investigators who lack the resources to perform the required evaluations of promising therapeutic compounds. Several compounds already are undergoing testing, including anti-hypertensive drugs, anti-inflammatory drugs, and novel small molecules. (Also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2.)

Similarly, NIH has developed several focused translational research initiatives over the last decade in the area of neurological disorders. The Spinal Muscular Atrophy (SMA) Project, for example, is an innovative pilot program to develop a treatment for spinal muscular atrophy using a "virtual pharma" strategy that engages resources to carry out a drug development plan via contracts and collaboration. The project has two patents on compounds that show promise and is evaluating the safety of the most promising drug candidates, with the goal of a human clinical trial beginning in 2010. (Also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2.)

Clinical Research: Learning Which Interventions Work

Clinical research helps scientists develop and test interventions and new treatments. There are many types of clinical research. For example, some observational clinical research studies involve following a group of patients with a condition and determining their symptoms and responses to treatment in order to refine medical practice. Some studies help researchers and clinicians determine whether dosing schedules, behavioral changes, and other elements of a treatment plan are realistic and appropriate. Clinical research sometimes overlaps with the category of epidemiological studies, which is

Clinical and Translational Research

described earlier in this chapter. These studies can help researchers develop new interventions that can be evaluated later in clinical trials.

Generally, clinical trials, particularly those evaluating drugs or medical devices, are conducted in phases, each of which helps scientists answer different questions. In a Phase I trial, researchers test an experimental drug or treatment in a small number of people (20-80) to evaluate its safety, determine a safe dosage range, and identify side effects. Phase II trials involve larger numbers of people (100-300) and evaluate the safety and effectiveness of the study drug or treatment. In Phase III trials, the experimental study drug or treatment is given to large numbers of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely. Phase IV, or postmarketing, studies are conducted to gather information associated with long-term use in various populations.

The randomized clinical trial has long been considered the gold standard for evaluating the effectiveness of investigational treatments. "Randomization" means that subjects are assigned by chance to either the investigational intervention or the control group. The control group might include interventions such as usual care; best proven care, if known; no treatment; or placebo. The specific clinical trial design is dependent upon the research questions posed. In addition to the use of control groups, clinical trials often use "blinded" or "masked" study designs, in which patient participants are purposely not told whether they are in the intervention or the control group. If feasible, clinical trials are often "double-blinded" or "double-masked," meaning that neither researchers nor participants know which people receive the intervention to ensure that the study results are unbiased.

Participation in clinical trials gives people an opportunity to contribute to the research effort and potentially gain early access to experimental treatments that might prove effective. For some participants, a study can provide expert medical care at a leading health care facility. Research risks and potential benefits are carefully balanced, and the burdens and benefits of participating are shared equally by appropriately including both sexes and people of all races/ethnicities and ages (see Appendix D). Balanced inclusion in trials allows investigators to know whether an intervention works equally well in different populations. NIH supports outreach efforts to recruit and retain children, women, and minorities in clinical studies. In addition, NIH recognizes the importance of developing sound scientific bases for pediatric care while protecting children adequately in research settings. NIH policy, therefore, requires that children (i.e., individuals younger than 21 years of age) be included in human subjects research conducted or supported by NIH, unless there are sound scientific or ethical reasons for excluding them. To help people access information about clinical trials for which they may be eligible, the ClinicalTrials.gov website offers general information about clinical trials and provides a searchable database of specific studies around the world.⁵⁴

NIH recognizes that the involvement of human beings as participants in research creates ethical and regulatory responsibilities for the investigators and institutions conducting such research. NIH clinical research encompasses the principles of respect for persons, beneficence, and justice. Most clinical research is federally regulated with built-in safeguards to protect the participants. NIH, therefore, has established a system of research, review, approval, and oversight to assist investigators in understanding ethical principles and complying with regulatory requirements to maximize safety for research subjects. The informed consent process is carefully designed to ensure that study participants understand the risks and possible benefits of the research. Various NIH initiatives and programs seek to harmonize regulatory aspects governing the conduct of clinical research to ensure that studies are conducted with scientific rigor, with minimal burdens on research subjects and investigators, and with utmost consideration for the safety, rights, and welfare of subjects. (See also *Ensuring Responsible Research* in Chapter 1.)

Fostering Collaborative NIH Clinical Research

NIH support and activities along the research continuum are enriching the pipeline of biomedical discoveries. NIH funnels the majority of its funding for clinical trials to its extramural partners, which operate at the regional, State, and local levels. Studies often are conducted at multiple institutions. Such multisite clinical trials help investigators quickly recruit enough

subjects for studies; give the public the widest possible access to clinical studies; and address the special health concerns of high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. To test investigational therapeutic and preventive strategies in the most expeditious way and hasten their entry into the clinic, NIH is supporting a wide variety of collaborations, research centers, and networks to conduct efficient multicenter clinical trials.

To investigate effective treatments for mental disorders, NIH uses its extensive clinical trials networks as platforms for research. The networks, which are maintained through infrastructure supported by NIH, evolved from a recent series of practical clinical trials. The networks comprise more than 60 sites throughout the United States that maintain continual outreach efforts to diverse groups of patients and families with mental illnesses. The Depression Trials Network, for example, is seeking participants for the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. This study will examine for the first time whether two different depression medications, when given in combination as the first treatment step, compared to one medication, will enhance remission rates, increase speed of remission, be tolerable to the participant, and provide better sustained benefits in the longer term.

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NIH equips networks of investigators with the tools they need for successful collaboration and information sharing. NIH supports many clinical research networks by funding ongoing infrastructure that provides means of standardizing data reporting to enable seamless data and sample sharing across studies. Through NIH-funded informatics and other technologies, researchers are better able to broaden the scope of their research and avoid duplicating research efforts, thereby freeing time and funds to address additional research questions.

Among the numerous networks established by NIH that have generated significant findings are the Maternal and Fetal Medicine Units Network, Neonatal Research Network, Obstetric Pharmacology Research Network, Collaborative Pediatric Critical Care Research Network, Pelvic Floor Disorders Network, Traumatic Brain Injury Clinical Trials Network, the Alzheimer's Disease Cooperative Study, and the Global Network for Women's and Children's Health Research. Additionally, the NCI Community Cancer Centers Program is encouraging more patient and physician involvement in NIH-sponsored cancer trials, establishing new methods for tracking minority accrual, and improving specimen collection. NIH recently has initiated several additional networks, including the notable examples of the Hepatitis B Clinical Research Network and the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network. These new networks are expected to generate significant findings in the future.

Addressing Gaps in Research

In terms of clinical evaluation of drugs, there is no clear line where NIH-supported work stops and the pharmaceutical industry picks up. Every drug candidate presents its own profile of benefit and potential for gains in public health as well as financial risk. NIH's aim is to be sure that all important leads are followed until they are mature enough to attract private-sector interest or until they reach a dead end. About half of the chemotherapeutic drugs currently used by oncologists for cancer treatment were discovered and/or developed by NIH. Cisplatin for treating testicular, ovarian, and lung cancer; paclitaxel (Taxol) for treating several different cancers; and fludarabine phosphate for treating lymphoma are examples of how NIH involvement in early-stage drug development led to products that were licensed to commercial organizations and reached the market. In addition, NIH involvement has been central in developing effective interventions for diagnosis, management, or monitoring of HIV/AIDS, tuberculosis, arthritis, malaria, and many other conditions.

Clinical and Translational Research

Government-funded research is particularly vital for the study of rare diseases. Not only do affected individuals benefit from new treatments that industry does not have the incentive to bring to market, but insights gained from such research often provide knowledge relevant to understanding more common diseases. For these reasons, NIH-funded investigators are studying an inherited retinal degenerative disease called Leber's congenital amaurosis (LCA), which causes severe vision loss in infancy or early childhood. NIH intramural scientists discovered that the *RPE65* gene plays a key role in the visual cycle—the set of biochemical interactions that converts light into an electrical signal to initiate vision. Mutations in this gene disrupt the visual cycle, resulting in LCA and blindness. As described in reports published in 2008 and 2009, an NIH-supported Phase I clinical trial of *RPE65* gene transfer in LCA found the treatment is safe and that visual function improved. Additional studies are exploring the range of therapeutic doses in adult and adolescent patients as well as rigorous evaluation of the effectiveness of this treatment. This clinical research is an important step in treating LCA and in establishing proof-of-concept for gene transfer as a therapy for eye disease.

Because behavioral interventions generally do not involve marketable products or services, NIH has a special role to play in research on how changes in behavior can improve health. For example, the Look AHEAD (Action for Health in Diabetes) study is examining the long-term health effects of an intensive lifestyle intervention (ILI) designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity. The study enrolled more than 5,100 overweight or obese adults with type 2 diabetes. Participants in the ILI group achieved clinically significant weight loss in the first year of the study; this was the case across all subgroups of the ethnically and demographically diverse study population. In addition, this weight loss was associated with an increase in health-related quality of life and improved cardiovascular fitness, blood pressure, cholesterol, and blood glucose levels, as compared to a control group receiving standard diabetes support and education. Look AHEAD seeks to determine whether the ILI reduces the incidence of heart attack and stroke, the leading causes of death among people with type 2 diabetes. This multicenter, randomized clinical trial involves several ICs as well as the Centers for Disease Control and Prevention.

The Look AHEAD (Action for Health in Diabetes) study is examining the long-term health effects of an intensive lifestyle intervention designed to achieve and maintain weight loss in overweight or obese people with type 2 diabetes through decreased caloric intake and increased physical activity.

One area where human research data often are lacking is the study of environmental effects on human health. Scientists working at the new Clinical Research Unit located on the NIH campus in Research Triangle Park, North Carolina, aim to narrow the gap between research and health care. The mission of the Clinical Research Unit is to translate basic laboratory findings to human studies; investigate interactions between genetic susceptibility and environmental factors in complex human traits and diseases; identify populations at risk; and develop novel preventive and therapeutic strategies to combat human diseases. Scientists who use the new facility are embarking on a diverse array of research studies involving pulmonary diseases, medical genetics, cardiovascular diseases, and reproductive health. The Clinical Research Unit also will provide advanced training opportunities for students and postdoctoral fellows whose research interests require access to clinical samples and patients.

Bariatric surgery is sometimes used in clinical practice as a treatment for severely obese adolescents despite a lack of evidence demonstrating its benefits for this population. NIH is addressing this research gap by supporting an observational study of teens already scheduled for surgery, Teen-LABS (Longitudinal Assessment of Bariatric Surgery). The Teen-LABS study is built upon the framework of the LABS consortium a group of surgeons, physicians, and scientists studying adult bariatric surgical outcomes. The Teen-LABS study will help determine whether bariatric surgery is an appropriate treatment option for extremely obese adolescents.

In response to another knowledge gap, NIH has launched the Clarification of Optimal Anticoagulation through Genetics (COAG) trial to gain a better understanding of the influences of clinical and genetic characteristics of patients in determining a safe and optimal dose of the drug warfarin, the most commonly used oral anticoagulant in the United States.

This prospective, multicenter, randomized clinical trial will recruit more than 1,200 patients who are beginning treatment with warfarin. The COAG study will help determine whether knowledge of some specific genes will help physicians find the safest, most effective warfarin dose for their patients. The drug is used to prevent dangerous blood clots that can potentially lead to pulmonary emboli and strokes, but the ideal dosage varies widely from one person to another. Getting the wrong amount of warfarin can be dangerous: If the dose is too high, patients could bleed profusely; if too low, life-threatening clots could develop. The knowledge gained in COAG will make significant scientific contributions to several medical specialties and help advance the field of personalized medicine.

Given the absence of a substantial commercial market, regulatory hurdles, and extensive clinical trial requirements, the private sector has little incentive to invest in biodefense measures. Biological weapons in the possession of hostile states or terrorists, as well as naturally occurring emerging and reemerging infectious diseases, are among the greatest security challenges to the United States. NIH, therefore, is fostering unique partnerships among government, industry, small businesses, and academia to facilitate the movement of promising products through all stages of the drug research and development pipeline, with the goal of developing vaccines and therapeutics against such biological threats as smallpox; botulism; Ebola, Marburg, and West Nile virus; avian influenza; and plague. (Also see the section on *Infectious Diseases and Biodefense* in Chapter 2.)

Putting Clinical Research Results into Practice

Throughout this report are descriptions of important studies that are changing the way health care is practiced in this country, improving public health and enhancing well-being. To fully realize the potential of new interventions, research results must be disseminated and put into widespread use. NIH carries out comparative effectiveness research (CER), investigates strategies for adoption of new evidence at the community level, trains health care providers in research skills, disseminates information to providers and the public based on the latest research findings, and sponsors research to learn about the most effective ways to disseminate such findings.

Comparing the Effectiveness of Different Therapies or Strategies

CER is the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in real-world settings. The purpose of such research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers about which interventions are most effective for which patients under specific circumstances. To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations and sub-groups. Defined interventions compared may include medications, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, and delivery system strategies. This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness and actively disseminate the results.⁵⁵

In efficacy research, such as a drug trial for FDA approval, the question typically is whether the treatment is efficacious under ideal, rather than real-world, settings. The results of such studies, therefore, are not necessarily generalizable to all patients or situations. CER is intended to complement this approach by helping patients and clinicians make decisions about which treatment is the best choice in given situations. CER also is called patient-centered health research or patient-centered outcomes research to illustrate its focus on patient needs.⁵⁶

NIH has a long history of supporting landmark CER studies that challenge existing standards of clinical practice. NIH was awarded \$400 million from the American Recovery and Reinvestment Act of 2009 (ARRA) for CER. A CER Coordinating Committee has been initiated to ensure optimal use of the recovery funds, make funding recommendations to the NIH Director, and develop a long-term CER research plan.

NIH investments are generating CER findings of public health significance, high relevance to clinical medicine, and scientific excellence. For example, the Spine Patient Outcomes Research Trial (SPORT) has helped answer questions

Clinical and Translational Research

about how best to treat various types of chronic low-back pain. Before SPORT, patients and physicians lacked data that compared treatment outcomes that could be used to guide people who were conflicted about whether to undergo surgery; some were not sure surgery was worth the risk, and others feared that delaying surgery might cause even more damage. SPORT has demonstrated that, indeed, surgery is superior to nonoperative treatments for the most common causes of chronic, severe low back pain: intervertebral disk herniation and lumbar spinal stenosis with or without degenerative spondylolisthesis (the slipping of vertebrae). In addition, the study revealed that people who have one of these conditions are not subjecting themselves to further harm if they adopt a wait-and-see approach before committing to surgery.

The Spine Patient Outcomes Research Trial (SPORT) has helped answer questions about how best to treat various types of chronic low-back pain. This is an example of NIH's commitment to comparative effectiveness research.

CER studies are ideal for providing physicians with evidence-based guidance to help them identify the safest and most effective therapies for their patients. For example, the NIH-supported Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial simultaneously compared two cardiovascular treatment approaches and two diabetes control strategies to improve survival and to lower the risk of heart attacks and strokes. The study, published in 2009, demonstrated that neither early revascularization nor insulin sensitization was superior to the tested alternatives in terms of cardiovascular disease (CVD) event rates. However, among patients for whom bypass surgery was deemed to be the appropriate revascularization procedure, prompt revascularization reduced the rate of major, nonfatal CVD events such as heart attack and stroke.

Changing Clinical Practice

It is not enough merely to have the infrastructure needed to address the ambitious goal of implementing science-based interventions and practices in community settings. Strategies to encourage adoption of proven approaches and treatments also are needed, as well as ways to tailor such approaches to specific populations or even to individuals. For example, NIH has made significant advances in elucidating the scientific bases for the effects of several treatment approaches based on complementary and alternative medicine (CAM). However, results of a national survey designed to gauge the potential for CAM research to influence clinical practice revealed a need for more effective dissemination of research findings. Acupuncturists, naturopaths, internists, and rheumatologists were asked about their awareness of two major NIH-sponsored studies of acupuncture or glucosamine/chondroitin for treating osteoarthritis of the knee. According to the survey results published in 2009, more than half (59 percent) of the 1,561 respondents were aware of at least 1 of the 2 clinical trials, but only 23 percent were aware of both. Although CAM research has the potential to make a difference in both conventional and alternative medicine clinical practice, the survey points to the need to train all clinicians in interpretation and use of evidence from research studies and to improve the dissemination of research results.

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In addition, NIH supports 13 Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging to improve the health, quality of life, and productivity of middle-aged and older people. The centers work to facilitate translation of basic behavioral and social science to practical outcomes by developing new technologies and by stimulating new use-inspired research (that is, research focused on meeting a societal need, usually for a device to improve quality of life for certain populations). Roybal investigators have made several key discoveries. One center, for example, has developed tools and technologies for identifying older adults at risk for automobile crash involvement and is working with industry partners to develop and disseminate products based on these tools. Another center has developed an electronic in-home assessment tool to facilitate early detection of changes in health or memory. Companies have used this model to develop related products, and the model has spurred several new NIH-funded research projects, including the development of a new medication tracker for older adults.

The Pharmacogenetics Research Network (PGRN) is ushering in the era of personalized medicine. The goal of pharmacogenetics research is to enable doctors to move beyond the current, one-size-fits-all approach to treatment and toward prescribing the drugs and dosages that will work best for each person. NIH established the PGRN to study how genes affect the way a person responds to medicines. The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), a component of the PGRN, sponsors data-sharing consortia. The International Tamoxifen Pharmacogenetics Consortium is gathering genetic and clinical data on the efficacy and toxicity of tamoxifen from patients around the world to test for specific associations between genetic variants and clinical effects. The International Severe Irinotecan Neutropenia Consortium is assembling a large data set to definitively answer questions relating to genetic effects on adverse outcomes of irinotecan anticancer therapy and to provide tools for evaluating toxicity risk.

Disseminating Research Findings

NIH produces the PubMed/MEDLINE database, the world's most heavily used source of information about research findings published in journal articles. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.) NIH also is taking the lead in special efforts to inform the public and health care practitioners about research results that have the potential to improve health (also see the section on *Health Communication and Information Campaigns and Clearinghouses* in Chapter 3). The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational materials on diabetes and kidney disease, respectively. For example, the NDEP disseminates the results of the DPP by encouraging people to take small steps to prevent type 2 diabetes. The NDEP also promotes the importance of comprehensive diabetes control in an educational campaign, "Control Your Diabetes. For Life." The NKDEP encourages African American families to discuss kidney disease at family reunions, and also provides tools and resources for health care providers to coordinate care and improve patient outcomes for kidney disease. Both programs tailor materials for minority groups that are disproportionately burdened by kidney disease, type 2 diabetes, and obesity.

In keeping with the NIH Public Access Policy (also see the sections on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3), scientists are required to submit final, peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central. This practice ensures that the public has access to the published results of NIH-funded research to help advance science and improve human health.

Located in the NIH Office of the Director, the Office of Medical Applications of Research (OMAR) works closely with ICs to assess, translate, and disseminate the results of biomedical research that can be used in the delivery of health services. OMAR coordinates periodic consensus conferences with the goal of reviewing areas of NIH-supported research where there may be a gap between research accomplishments and clinical care. To date, NIH has conducted more than 120 consensus development conferences and 30 state-of-the-science conferences. Consensus and state-of-the-science statements are disseminated widely after the conference either to modify clinical practice when evidence strongly supports the use (or avoidance) of a particular intervention or to direct future research when important gaps in knowledge have been identified. The consensus statements that result from these conferences are shared widely with health care providers, policymakers, patients, and the media. In 2008, consensus statements were issued on hydroxyurea treatment for sickle cell disease and on the management of hepatitis B. In 2009, state-of-the-science statements were released on the use of family histories in the primary care setting and on the diagnosis and management of ductal carcinoma in situ.

In its quest to help clinicians and patients make appropriate decisions about health care, NIH periodically convenes expert panels that review the cumulative research and publish evidence-based clinical practice guidelines that describe a range of generally accepted approaches for the diagnosis, management, or prevention of specific diseases or conditions. In addition, NIH clinical guidelines provide recommendations that patients and their doctors can use to develop individual treatment plans tailored to the specific needs and circumstances of the patient. In 2009, two new guidelines for the prevention and treatment of HIV-associated co-infections were issued: *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents* and *Guidelines for the Prevention and Treatment of Opportunistic*

Clinical and Translational Research

Infections Among HIV-Exposed and HIV-Infected Children. The Pediatric Cardiovascular Risk Reduction Initiative guideline is slated for release in mid 2010.

In its quest to help clinicians and patients make appropriate decisions about health care, NIH periodically convenes expert panels that review the cumulative research and publish evidence-based clinical practice guidelines. The Pediatric Cardiovascular Risk Reduction Initiative guideline is slated for release in mid-2010.

Bolstering the Research Continuum

NIH is committed to restructuring the clinical research enterprise, a key objective of the NIH Roadmap for Medical Research, which comprises a series of initiatives funded by the NIH Common Fund. These high-impact initiatives are designed to pursue major opportunities and gaps in biomedical research that no single NIH institute could tackle alone, but which the agency as a whole can address to make the biggest impact possible on the progress of medical research. To accelerate and strengthen the clinical research process, a set of NIH Roadmap initiatives will work toward improving the clinical research enterprise by adopting a systematic infrastructure that will better serve the evolving field.

Building Capacity for Clinical and Translational Research

Drawing on the momentum of the NIH Roadmap and extensive community input, the Clinical and Translational Science Award (CTSA) program is creating academic homes for the discipline of clinical and translational science at institutions across the country. As of fall 2009, this network of research institutions consists of 46 awardees in 26 states. The consortium will eventually link about 60 institutions around the Nation. The program encourages the development of novel methods and approaches to clinical and translational research, enhances informatics and technology resources, and improves training and mentoring to ensure that new investigators can navigate an increasingly complex research system. CTSA's are enabling researchers to work in unprecedented ways to advance medical research across many disease areas and conditions, including cancer, neurological diseases, cardiovascular disease, diabetes, and obesity.

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A key ingredient in research success is the translation of laboratory bench insights to the patient bedside and back again, to inspire new laboratory investigations that ultimately improve patient care and public health. In this vein, the Centers of Research Translation (CORT) program was launched to unite basic and clinical research. Each CORT encompasses at least three projects, including one clinical and one basic research study. The three most recently funded CORTs are the Center for Genetic Dissection of SLE (lupus), the Center for New Approaches to Assess and Forestall Osteoarthritis in Injured Joints, and the Center for Psoriasis Research Translation.

Researchers are increasingly conducting studies in community clinics, doctors' offices, and other health care facilities as innovative means of building capacity across the Nation and ensuring that diverse populations are involved in research. For example, NIH fosters scientifically rigorous research in oral health care in three dental practice-based research networks (PBRNs) to address the longstanding lack of high-quality research data to guide everyday treatment decisions in the dentist's office. The PBRNs have developed multiple methods of delivering research training to practicing clinicians, including training in research methods, protection of human participants, good clinical practice, research protocol development, and interpretation of research results. Descriptions of the training programs have been reported in national journals, and a collaboratively written chapter recently was accepted for publication in a textbook on PBRNs. Over the course of the grant period, the networks will each complete approximately 15 to 20 short studies, several of which have already been reported in the scientific literature.

Developing the Research Teams of the Future

Through its career development initiatives, NIH is preparing to meet the need for a multidisciplinary, well-trained cadre of researchers at every point in the research continuum. (Also see the section on *Research Training and Career Development* in Chapter 3.) For example, a key component of the CTSA program is the creation of graduate degree-granting and postgraduate programs in clinical and translational science, which will provide an enriched environment for educating and retaining the next generation of clinical and translational researchers.

In addition, NIH develops, administers, and evaluates clinical research training initiatives that contribute to the professional growth of the clinical and translational research community, including medical and dental students, physicians in residency and in fellowship programs, established investigators, allied health professionals, and community partners. A clinical research curriculum is offered at NIH and other domestic and international locations. Extramural researchers have a new opportunity to access rich training experiences via a "Clinical Research Management Sabbatical," designed to help them develop leadership skills for conducting clinical research. Partnerships between NIH and extramural collaborators and industry have contributed to the menu of educational offerings. For example, via videoconferencing, Duke University School of Medicine offers NIH physicians and dentists an opportunity to receive a master's degree of health sciences in clinical research. The intramural Clinical Research Training Program, a partnership supported by NIH and a grant to the Foundation for the NIH from Pfizer, Inc., trains 30 advanced medical and dental students annually in clinical or translational research.

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The Research Centers in Minority Institutions (RCMI) program develops and enhances the research infrastructure of minority institutions by expanding human and physical resources for conducting basic, clinical, and translational research. The program, which began in 1985 in response to congressional report language (see the description of the RCMI program in the notable examples that follow under the theme "Bolstering the Research Continuum"), provides grants to institutions that award doctoral degrees in the health professions or health-related sciences and have enrollments that are predominantly students from minority communities underrepresented in the biomedical sciences. The RCMI Translational Research Network (RTRN) is a national consortium of clinical and translational researchers in the RCMI Centers, working in collaboration with investigators from other academic health centers, community health providers, and the public to focus their collective efforts on addressing health disparities. RTRN researchers focus on diseases that disproportionately affect minority and other medically underserved populations. The multisite collaborative research supported by RTRN infrastructure, training, and resources is ensuring that discoveries generated in the laboratory are being translated into clinical studies. (Also see the section on *Minority Health and Health Disparities* in Chapter 2.)

The RCMI Clinical Research Education and Career Development (CRECD) Awards provide didactic training and mentored clinical research experiences to develop independent researchers who can lead clinical research studies, especially those addressing health disparities. RCMI CRECD awards help develop and implement degree programs in minority institutions that train doctoral and postdoctoral candidates in clinical research.

Improving Research Efficiency

Maximizing human subject protection, while facilitating translational and applied clinical research, has become a critical challenge in the 21st century. To increase the efficiency and effectiveness of the clinical research enterprise, NIH is examining barriers to clinical research and striving to harmonize regulations and policies that pertain to its conduct and oversight.

Clinical and Translational Research

The NIH Clinical Research Policy Analysis and Coordination (CRpac) program is a focal point for streamlining and optimizing policies and requirements concerning the conduct and oversight of clinical research.

The NIH Clinical Research Policy Analysis and Coordination (CRpac) program is a focal point for streamlining and optimizing policies and requirements concerning the conduct and oversight of clinical research. As the lead Federal agency supporting clinical research, it is incumbent upon NIH to promote the efficiency and effectiveness of the clinical research enterprise by facilitating compliance and oversight. The CRpac program works on an array of issues and activities usually in close collaboration with other Federal agencies and offices that have responsibilities concerning the oversight of clinical research. NIH also is partnering with several other Federal agencies to ensure that a standard reporting format is available for investigators to report adverse events associated with their clinical research. The development of the Basal Adverse Event Report (BAER) will allow investigators to satisfy the different safety reporting requirements for all Federal agencies. NIH also has specific initiatives to restructure the clinical trials enterprise in the area of oncology. For example, the Standard Terms of Agreement for Research Trials are designed to help cut the time spent on contract negotiations between pharmaceutical/biotechnology companies and academic medical centers. In addition, the Clinical Trials Reporting Program is establishing a comprehensive database containing regularly updated information on all NCI-funded interventional clinical trials. Grantees are requested to enter specific information about each clinical trial into the database. This information will be used to coordinate research efforts to optimize the Nation's investment in cancer research.

Conclusion

The results of NIH's commitment to clinical and translational science are apparent in the following highlights describing some of the important accomplishments and ongoing initiatives in these rapidly developing areas of research.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research

I = Supported through **I**ntramural research

O = **O**ther (e.g., policy, planning, or communication)

COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program

GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct

ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Preclinical Research: Translating Basic Science Discoveries to Human Studies

New Therapeutic Strategy for Retinitis Pigmentosa: Retinitis pigmentosa (RP) is a set of genetic diseases that cause the death of rod photoreceptors, the light-sensitive cells in the peripheral retina that help us see in dark and dimly lit environments. Unfortunately, the death of rod cells causes the death and degeneration of healthy cone cells. Cone photoreceptors provide sharp visual acuity, allowing us to read, recognize faces, drive a car, or perform other daily tasks that require hand-eye coordination. If cone cells could be preserved, patients with RP could avoid severe impairment. Mounting evidence suggests that cone cells die due to oxidative damage because the blood vessels in the retina cannot regulate blood flow to reflect decreased oxygen demand after rod cell death. NIH-supported investigators recently began efforts to bolster innate production of antioxidants by overexpressing genes that defend against oxidative assault. In a novel set of experiments, investigators developed a mouse strain with RP that also overexpressed various genes involved

in the antioxidant defense system. Overexpression of superoxide dismutase 2 (SOD2) and catalase, two powerful antioxidant enzymes, preserved cone cells. These findings support the concept of a gene-based treatment strategy to strengthen the body's antioxidant defense system in patients with RP.

- Usui S, et al. *Mol Ther* 2009;17(5):778-86. PMID: 19293779.
- For more information, see <http://www.nature.com/mt/journal/v17/n5/abs/mt200947a.html>
- (E) (NEI)

Translational Research on Alzheimer's Disease (AD): To move basic research on AD and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. A number of agents are undergoing testing, including antihypertensives, anti-inflammatory drugs, and novel small molecules. In addition, in recent years, NIH-supported basic research has contributed to industry development of new Alzheimer's disease drugs. This program is a cornerstone of the NIH GPRA goal to "by 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-048.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIA) (GPRA)

Lupus: There have been significant advances in identifying disease risk genes for systemic lupus erythematosus (lupus) in recent years. Genome-wide association, linkage analysis, and direct sequencing have revealed genetic variations in lupus patients for molecules involved in immune mechanisms and regulation, inflammation, and vascular cell activities. The disease affects women disproportionately, with female lupus patients outnumbering males nine to one. African American women are three times as likely to get lupus as Caucasian women, and it also is common more in Hispanic, Asian, and American Indian women. These results are being replicated in distinct racial and ethnic populations. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects. Another critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by government agencies, private foundations, and industry. The numerous genes uncovered in these studies reflect the complex expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene specifically is associated with severe forms of lupus that include kidney disease, but not skin manifestations. Methods to analyze patients' blood samples are being developed to group disease-specific variations in gene expression according to pathogenic mechanisms. This system may be used to predict flares of lupus activity in the future and guide individualized treatment. Lupus risk genes also have been discovered on the X chromosome and reproduced in animal models of the disease. These important findings shed light on the female predominance of lupus.

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- Jacob CO, et al. *Proc Natl Acad Sci U S A* 2009;106(15):6256-61. PMID: 19329491. PMCID: PMC2669395.

Clinical and Translational Research

- This example also appears in Chapter 2: *Autoimmune Diseases*, Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*
- (E/I) (NIAMS, NCI, NCRR, NHLBI, NIAID, NIDCR, NINDS)

Addressing the Heterogeneity of Autism Spectrum Disorders: NIH released a series of Funding Opportunity Announcements (FOAs), supported by funds from the American Recovery and Reinvestment Act of 2009, soliciting applications for 2-year research projects to address the heterogeneity of Autism Spectrum Disorders (ASD). This initiative represents the largest NIH funding opportunity for research on ASD to date and will jump-start many of the short-term objectives set forth in the Interagency Autism Coordinating Committee's Strategic Plan for Autism Spectrum Disorder Research. The FOAs target research in areas such as measurement development, biomarkers, immune and central nervous systems interactions, genetics, environmental risk factors, model development, treatment and intervention, and services research.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-170.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-171.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-172.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-173.html>
- For more information, see <http://www.nimh.nih.gov/science-news/2009/rising-to-the-challenge-nih-will-use-60-million-in-recovery-act-funds-to-support-strategic-autism-research.shtml>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIMH, NICHD, NIDCD, NIEHS, NINDS) (ARRA)

Pediatric Rheumatic Diseases: A rare, genetically inherited, inflammatory condition recently was discovered by researchers from NIH and other institutions. DIRA ("deficiency of the interleukin-1 receptor antagonist") patients often are misdiagnosed and do not receive appropriate treatment because their disease is characterized by symptoms seen in many illnesses: recurring episodes of systemic inflammation in multiple tissues, such as skin, bones, and joints. Inflammation is crucial in fighting infections, but uncontrolled, chronic inflammation can cause organ and tissue damage. It was found that DIRA symptoms are caused by a defective gene for a protein (IL-1Ra) that normally inhibits molecular signals for inflammation. Understanding DIRA symptoms and pathogenesis can guide better treatment for the disease, and may help clarify the IL-1Ra gene's role in promoting inflammation in more common diseases. On another front, children with lupus have a significantly increased risk for cardiovascular complications related to premature atherosclerosis, which is a 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. Statins also have intrinsic anti-inflammatory properties. The Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial has been testing whether statins can delay the progression of arterial thickening from atherosclerosis in children diagnosed with lupus. Another prospective study of adult and pediatric lupus patients confirmed previous observations, that children have more active disease than adults at the time of diagnosis. Over time, pediatric lupus patients also have more aggressive and severe disease than adult lupus patients.

- Aksentijevich I, et al. *N Engl J Med* 2009;360(23):2426-37. PMID: 19494218. PMCID: PMC2876877.
- Brunner HI, et al. *Arthritis Rheum* 2008;58(2):556-62. PMID: 18240232.
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2009/06_03.asp
- This example also appears in Chapter 2: *Autoimmune Diseases*
- (E/I) (NIAMS)

New Indications for Established Agents to Treat Chronic Disease: When identifying interventions to treat an illness or chronic condition, testing drugs that already have been developed for other conditions sometimes can be faster and more cost-effective than designing entirely new agents because drug safety profiles already have been established, and contraindications already are known. NIH intramural investigators currently are exploring the use of several established agents in the treatment of chronic disease. For example, a growing body of animal research suggests that the compound fenoterol, widely used for treatment of pulmonary disease, may be effective in the treatment of congestive heart failure. Experimental results with fenoterol are sufficiently encouraging to recommend advancing translational efforts and planning clinical trials. Other studies in animal models have shown that the drug erythropoietin, used to treat certain types of anemia, has a protective effect on the heart if administered shortly after a heart attack. Based on the results of these studies, researchers have initiated a study to assess the effects of erythropoietin (EPO) on the heart after a heart attack. Researchers also have reported preclinical data that suggest a therapeutic benefit of the diabetes drug exendin-4 in the treatment of stroke and Parkinson's disease.

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (I) (NIA)

NIH Countermeasures Against Chemical Threats (CounterACT) Research Program: The CounterACT Research Network, as reflected in an NIH GPRA goal, develops medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The Network, which has collaborated with the U.S. Department of Defense (DOD) from its inception in 2006, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. One promising countermeasure, midazolam, which DOD researchers identified as a potential countermeasure against chemical agent-induced seizures, has entered clinical trials through the NIH Neurological Emergency Clinical Trials Network, and NIH is collaborating with DOD to complete animal studies necessary for its FDA approval as a nerve agent treatment. The New Drug Application is expected early FY 2010, with approval anticipated by the end of the year. The Network also has developed six other lead compounds as therapeutics for cyanide, nerve agent, chlorine, and sulfur mustard, and has participated in pre-Investigational New Drug application meetings with FDA related to these efforts. One of the diagnostic devices developed by the program is being used in an NIH clinical trial. Three chemical agent therapeutics developed by the program also show promise as therapies for radiation exposures, and the program is collaborating with the NIH Medical Countermeasures Against Radiological and Nuclear Threats program.

- For more information, see http://www.ninds.nih.gov/research/counterterrorism/counterACT_home.htm
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00809146>
- For more information, see <http://nett.umich.edu/nett/welcome>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NINDS, NEI, NIAID, NIAMS, NICHD, NIEHS, NIGMS) (GPRA)

Peripheral Neuropathies: NIH funds studies focused on understanding the genetic basis and molecular and cellular mechanisms of many peripheral neuropathies, including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, inherited neuropathies such as Charcot-Marie-Tooth, inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy, and rare forms of peripheral neuropathy. Other notable projects include a natural history study of diabetic neuropathy, projects to improve the efficiency and effectiveness of diagnosis for various peripheral neuropathies, and a Phase III clinical trial to treat Familial Amyloidotic Polyneuropathy. In August 2008, a pair of program announcements was released to promote translational research in neuromuscular disease. Diseases included in these program announcements are those that affect the motor unit—the motoneuron, its process (axon), and the skeletal

Clinical and Translational Research

muscle fiber that is innervated by the neuron—such as peripheral neuropathy, amyotrophic lateral sclerosis, and muscular dystrophy. This unique structure-function framework provides a coordinated approach for therapeutic development in a subset of neurological diseases that share many common features, including the peripheral neuropathies.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NINDS, NIDDK)

Programs to Accelerate Medication Development for Alcoholism Treatment: Alcohol dependence is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ among individuals. Therefore, a diverse repertoire of medications is needed to provide effective therapy to a broad spectrum of alcohol-dependent individuals. Although promising compounds have been identified, developing medications is a long and costly process with a low probability of success for any single agent. NIH has initiated collaborations with the pharmaceutical industry to ensure its interest in taking promising compounds through the final phase of clinical trials and subsequent FDA consideration. As part of this approach, two new programs have been initiated:

- Laboratories have been established to screen promising compounds with animal models, enabling faster determination of those that merit advancement to large, multisite studies. Animal studies already have produced several targets for human studies that now are underway. The animal models are being validated using medications that have been tested clinically.
- A network of sites is being developed to conduct early Phase II proof-of-concept human trials. NIH will encourage the pharmaceutical industry to screen proprietary compounds in the preclinical models and, when results are positive, test them in the early Phase II human trials network. Currently quetiapine and levetiracetam are being evaluated in this network.
- Pharmacogenetic studies are ongoing to determine genetic variants that predict success for various medications.

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E/I) (NIAAA) (GPRA)

Translational Research with Gene Transfer for X-Linked Juvenile Retinoschisis (XLRS), a Congenital Eye Disease of Boys: XLRS is a rare but severe developmental abnormality of the retina found in children that causes impaired visual acuity and retinal detachment. Clinical examination shows small cysts within the macula, the center of the retina, and a splitting (or schisis) of the layers of the peripheral retina. XLRS is caused by a mutation in a single gene, retinoschisin, which is thought to play a structural role in the retina. NIH intramural investigators are developing gene transfer therapy to ameliorate and possibly cure XLRS. In other gene transfer clinical trials for Leber congenital amaurosis, a single subretinal injection of the gene-carrying vector reached about 25 percent of the retina. However, subretinal injection is unsuitable for XLRS as the retina is too fragile and the entire retina needs treatment to prevent further schisis. To this end, NIH intramural investigators injected a vector containing copies of the retinoschisin gene into the vitreous, the clear, jelly-like fluid inside the eye, using a mouse model of XLRS. This allowed retinoschisin to penetrate the entire retina in amounts similar to healthy retinas. Treated mice demonstrated a decrease in schisis and showed improved retinal activity 11-15 weeks after treatment. This study offers evidence that injection into the vitreous is a viable method to deliver gene therapy to the neural retina.

- Park TK, et al. *Gene Ther* 2009;16:916-26. PMID: 19458650. PMCID: PMC2774250.
- For more information, see <http://www.nature.com/gt/journal/v16/n7/full/gt200961a.html>
- (I) (NEI, NIDCD)

The NIH Rapid Access to Intervention Development (RAID) Program: The NIH-RAID program makes available, on a competitive basis and at no cost to investigators, certain critical resources needed to develop new therapeutic agents, including not only laboratory services but also expertise in the regulatory process. The program directly addresses roadblocks to moving research findings from bench to bedside. Among the projects approved are potential therapies for hepatic fibrosis, sickle cell anemia, drug abuse, and Crohn's disease. The NIH-RAID program is part of the NIH Roadmap for Medical Research.

- For more information, see <http://nihroadmap.nih.gov/raid/index.aspx>
- (E) (NINDS, Common Fund - all ICs participate)

Translational Research for Neurological Disorders: The Anticonvulsant Screening Program has catalyzed the development of six epilepsy drugs now on the market; the Neural Prosthesis Program has pioneered devices to restore lost nervous system functions; the Intramural Program has developed the first enzyme therapy for inherited disorders; and investigator-initiated research programs have led to development of FDA-approved drugs by industry. In 2003, NIH launched a program designed to expedite preclinical therapy development across all neurological disorders. The Cooperative Program in Translational Research supports academic and small business investigator-initiated projects in single laboratories or consortia, using milestone-driven funding and peer review tailored to the requirements of therapy development. Projects are developing drug, stem cell, or gene therapies for amyotrophic lateral sclerosis (ALS), Batten disease, epilepsy, Huntington's disease, muscular dystrophies, Parkinson's disease, tuberous sclerosis, and stroke, among other disorders. NIH also has developed several focused translational research initiatives over the last decade. The Spinal Muscular Atrophy (SMA) Project, for example, is an innovative pilot program to develop a treatment for SMA using a "virtual pharma" strategy that engages resources to carry out a drug development plan via contracts and collaboration. The project has two patents on compounds that show promise and is evaluating the safety of the most promising drug candidates, with the goal to begin human clinical trials as soon as possible. Translational research is a "signature project" for NINDS investment of American Recovery and Reinvestment Act funds.

- For more information, see <http://www.ninds.nih.gov/funding/research/translational/index.htm>.
- For more information, see <http://www.ninds.nih.gov/research/asp/index.htm>
- For more information, see <http://www.ninds.nih.gov/research/translational/index.htm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NINDS) (ARRA)

Confronting the Challenge of Antimicrobial Resistance: Antimicrobial resistance has become a major public health threat that is severely jeopardizing the utility of many "first-line" antimicrobial agents. The development of resistance can be caused by many factors, including the inappropriate use of antibiotics. NIH supports a robust basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes. NIH also is pursuing translational and clinical research in this area, including clinical studies to test interventions for community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection and to evaluate the efficacy of off-patent antimicrobial agents. NIH laboratories are at the forefront of understanding the fundamental causes of resistance—from studies of the disease-causing organisms and the progression of disease to research on the advantages and shortcomings of current antibiotics. Specific research foci of NIH researchers and NIH-supported grantees include MRSA and vancomycin-resistant *Staphylococcus aureus* (VRSA) (commonly acquired in community settings), and drug-resistant malaria and tuberculosis. NIH supports genomic sequencing through its Microbial Sequencing Centers; researchers at these centers have sequenced the genomes of numerous disease-causing bacteria, viruses, parasites, and fungi, which may help identify mechanisms of resistance and when and where resistance emerges.

Clinical and Translational Research

- For more information, see <http://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Genomics*
- (E/I) (**NIAID**) (GPRA)

Development and Testing of Malaria Vaccines and Therapeutics: NIH supports recent calls to work toward the goal of malaria eradication. Means toward this end include stopping the spread of the malaria parasite, reducing the burden of disease region by region, and eliminating the parasite from malaria-endemic countries and then from every country throughout the world. In FY 2008, NIH assessed its malaria research portfolio and identified opportunities for the next phase of malaria research. This led to the publication of the Strategic Plan for Malaria Research and the related NIAID Research Agenda for Malaria. NIH recently launched a new initiative, the International Centers of Excellence in Malaria Research, to support a novel, global, multidisciplinary approach to understanding malaria in the evolving context of control, elimination, and eradication. NIH researchers recently began clinical investigations to assess malaria biology and pathogenesis with collaborators in Mali and Cambodia, activities that resulted in the completion (or expansion) of research facilities and hospitals to support new malaria research programs. Examples of NIH-supported advances in malaria research include:

- Successfully decoding the genome of the parasite that causes relapsing malaria and determining that the anti-malarial drug, chloroquine, may once again be used to prevent malaria in African children.
- Investigating novel vaccine strategies, such as those that block transmission of the malaria parasite to the mosquito vector, and exploring the molecular biology of the parasite and its interaction with humans.

Ten vaccine candidates currently are in preclinical development and five are in clinical trials.

- For more information, see <http://www3.niaid.nih.gov/topics/Malaria/>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E/I) (**NIAID**)

Medical Countermeasures Against Nuclear and Radiological Threats: NIH continues to lead the HHS effort to sponsor and coordinate research to develop medical countermeasures to mitigate and/or treat radiation-induced damage. Many candidate medical countermeasures are in the early stages of discovery; however, substantial effort focuses on later development as lead compounds are identified. Animal model testing is underway for 59 medical countermeasures for hematopoietic (HE) acute radiation syndrome (ARS), 18 for gastrointestinal (GI) ARS, 13 for radiation-induced lung pneumonitis and/or fibrosis, 13 for kidney injury, 7 for brain injury, and 17 for skin, including combined injuries (radiation plus burns or wounds). Three orally bioavailable forms of diethylenetriaminepentaacetic acid (DTPA), which may be used to treat victims with internal radionuclide contamination from fallout or "dirty bombs," are in development. Research into 6 lead, orally bioavailable compounds with enhanced properties for removing radioactive isotopes from the body also is ongoing. Interactions with 87 biotechnology companies through an advanced development contract have led to the identification and initial animal efficacy confirmation for 7 HE-ARS candidate medical countermeasures and 2 GI-ARS candidate medical countermeasures. Other areas of research include characterization of genomic, proteomic, metabolomic and cytogenetic markers of radiation injury, and development of biodosimetry devices to provide accurate and timely radiation exposure information to assist in medical triage and treatment strategies.

- For more information, see <http://www3.niaid.nih.gov/topics/radnuc/>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (**NIAID**) (ARRA)

Rapid Research Response to Emerging Disease Threats: The sudden and unpredictable emergence of infectious diseases requires advance preparation to safeguard public health. Because the groundwork of basic research can be crucial when new health threats arise, NIH conducts and supports research to increase basic knowledge of infectious diseases, and advance development of effective diagnostics, therapeutics, and vaccines. In the case of severe acute respiratory syndrome (SARS), for instance, NIH's broad portfolio of basic research grants on coronaviruses was critical to understanding the new pathogen. NIH has developed new funding initiatives for accelerated, targeted research to encourage collaborative and product development-oriented projects. NIH also provides needed infrastructure and resources to support the research community in the event of a public health emergency. For example, the national network of Vaccine and Treatment Evaluation Units provides a ready means to conduct clinical trials to evaluate vaccines and treatments for outbreaks such as the novel 2009 H1N1 influenza. In 2009, NIH awarded new funding for 1 and renewed funding for 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs). The RCEs are a critical component of the U.S. research infrastructure for infectious diseases, and are designed to respond flexibly to changing scientific needs and priorities. RCE researchers are developing new or improved ways to treat, diagnose, or prevent illnesses, including anthrax, West Nile fever, plague, and dengue fever. The RCEs are prepared to provide scientific expertise to first responders in an infectious disease-related emergency, whether such an emergency arises naturally or through an act of bioterrorism.

- For more information, see <http://www3.niaid.nih.gov/LabsAndResources/resources/rce/default.htm>
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/RCEs_ARRA.htm
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E/I) (NIAID) (ARRA)

Renewed Focus on Basic HIV Vaccine Discovery Research: In March 2008, NIH sponsored a Summit on HIV Vaccine Research and Development. Participants reached consensus that NIH should increase its emphasis on basic vaccine discovery research. Toward this end, the Highly Innovative Tactics to Interrupt Transmission of HIV program was established to stimulate research on novel, unconventional, "outside the box," high-risk, high-potential, and high-impact approaches that might provide long-term protection from HIV acquisition. The Basic HIV Discovery Research initiative also was initiated to support generation of knowledge that will inform new conceptual approaches to HIV vaccine design. NIH also funds new research through the B Cell Immunology for Protective HIV-1 Vaccine program to foster fundamental research on B cell immunology to derive new understanding and approaches for development of HIV vaccines. NIH continues to conduct clinical research as appropriate and seeks to answer basic research questions through clinical trials. NIH recently launched an exploratory clinical trial through the HIV Vaccine Trials Network to examine whether a two-part vaccine regimen can decrease viral load in vaccinated male study participants who later become infected with HIV. It is hoped that this study will answer important scientific questions that could lead to the discovery and development of new and improved HIV vaccine candidates.

- For more information, see <http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/research/>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-024.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIAID) (GPRA)

Tackling Neglected Tropical Diseases: Neglected tropical diseases (NTDs) such as lymphatic filariasis, schistosomiasis, leishmaniasis, and dengue take a tremendous toll on global health. The World Health Organization estimates that more than 1 billion people—approximately one-sixth of the world's population—suffer from at least 1 NTD. NIH scientists and NIH-supported researchers in countries where NTDs are widespread are developing vaccines and treatments for diseases such as leishmaniasis and identifying new drugs for sleeping sickness and Chagas' disease. NIH-supported researchers also have made a significant leap forward in the battle against schistosomiasis by identifying potential new therapies through the use of genomics and medicinal chemistry. The Vector Biology Research Program supports research

Clinical and Translational Research

on several vectors that transmit agents of NTDs. Through this program, a project in French Polynesia aims to reduce populations of *Aedes polynesiensis*, a mosquito species responsible for spreading filariasis. Other investigators studying the mosquito immune response against filarial worms hope to identify targets for blocking development of the worm inside the mosquito. NIH scientists studying the salivary proteome of NTD vectors are identifying novel biologically active compounds and vaccine targets. In FY 2009, NIH-supported researchers reported the first complete genome sequences for two parasite species that cause schistosomiasis. Finally, a public-private partnerships for product development program is designed to accelerate research and development of new diagnostic, preventive, therapeutic, and control strategies for infectious diseases of global importance for which commercial markets currently provide insufficient incentive for corporate investment.

- For more information, see <http://www3.niaid.nih.gov/topics/tropicalDiseases/default.htm>
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/schisto_genomes.htm
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E/I) (NIAID)

Three-Pronged Approach to Fighting HIV: The unique and formidable challenge of combating HIV is spurring leaders in medicine and public health to consider a bold new approach to fighting it. NIH and other organizations are exploring a three-pronged approach to fight the HIV/AIDS pandemic. The first prong is pre-exposure prophylaxis (PrEP), which uses antiretroviral therapies to prevent HIV infection among people who are not infected with HIV but who are at high risk of becoming infected. NIH currently is testing this approach in clinical trials such as the iPREX study, which is examining whether the HIV treatment Truvada can prevent HIV infection among HIV-negative men who have sex with men. The second prong is a novel approach, based on mathematical modeling, which suggests that the implementation of a universal HIV testing program and the immediate initiation of antiretroviral therapy (ART) for those individuals who test positive could dramatically reduce the number of new HIV cases within the decade. NIH now is addressing a number of critical scientific issues to determine the feasibility of this approach. Finally, NIH is strongly encouraging research to cure HIV by eliminating HIV reservoirs, pockets of undetectable latent and persistent HIV, which exist even in people on ART who have an undetectable viral load. Stopping ART treatment results in a rebound of viral load to levels seen prior to treatment. NIH has launched a new initiative to identify these reservoirs and develop techniques to eradicate them.

- Paltiel AD, et al. *Clin Infect Dis* 2009;48(6):806-15. PMID: 19193111.
- Dieffenbach CW, Fauci AS. *JAMA* 2009;301(22):2380-2. PMID: 19509386.
- For more information, see <http://www.washingtonpost.com/wp-dyn/content/article/2009/04/15/AR2009041503040.html>
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/test_treat.htm
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIAID) (ARRA)

2009 H1N1—Responding to Pandemic Influenza: NIH is engaged fully in the government-wide effort to understand the 2009 H1N1 virus and rapidly develop countermeasures. Activities are being conducted in NIH-supported research networks such as the Centers of Excellence in Influenza Research and Surveillance (CEIRS) and Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs), as well as by industry partners and individual NIH grantees. NIH used its longstanding vaccine clinical trials infrastructure—notably, the network of Vaccine and Treatment Evaluation Units—to quickly evaluate pilot lots of vaccine candidates for safety and ability to induce protective immune responses, and to determine the appropriate dose and number of dosages. Because of increased resistance to existing antiviral therapeutics, NIH is working to develop the next generation of influenza therapeutics/antivirals. Three drugs now in clinical testing include a long-acting neuraminidase inhibitor, an inhibitor of the enzyme that replicates viral genes, and a drug that prevents the virus from entering human lung cells. NIH will evaluate how well these candidate antiviral drugs block the 2009 H1N1 strain and will screen other compounds for activity against the virus. NIH also is developing

diagnostic platforms that can rapidly identify a wide variety of pathogens in clinical samples, including specific subtypes of influenza. NIH is accelerating development of these platforms to provide improved diagnostics for 2009 H1N1 influenza. In addition, enrollment is complete for an NIH pandemic influenza H1N1 DNA vaccine Phase I clinical trial that has begun, and NIH scientists are conducting basic research to develop universal influenza vaccines that can protect against multiple influenza strains.

- For more information, see <http://www3.niaid.nih.gov/topics/Flu/understandingFlu/2009h1n1.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E/I) (NIAID)

Preclinical Disease Models Informatics: Preclinical research results derived from animal models are an essential element in the decisional process to determine whether a basic science discovery should be considered as a potential therapeutic approach worthy of future development. Scientists who work with animal models can look forward to a new online tool designed to increase research efficiency, improve collaboration, and ultimately help bridge the gap between basic science and human medicine. With funding from NIH, the Linking Animal Models to Human Disease Initiative (LAMHDI) will integrate data and information about animal models and make them available to health researchers. LAMHDI creators will develop a database and website designed to make it easier for the biomedical research community to locate, identify, apply, and build upon the most useful animal models for its research. The initiative grew out of the Animal Models: Informatics and Access meeting in August 2008. At this meeting, animal research and informatics experts explored ways to remove research barriers and to develop frameworks for effective computation on existing animal models data to facilitate medical progress. The \$1.57 million NIH-funded project is supported by a contract to Turner Consulting Group, a strategy and information technology firm.

- For more information, see http://www.ncrr.nih.gov/publications/comparative_medicine/animal_models_informatics_and_access.asp
- (E) (NCRR)

Strategies to Manage and Prevent Food Allergies: Food allergy occurs in approximately 4.7 percent of children under 5 years of age and in 3.7 percent of children 5 to 17 years of age. Allergies to peanuts and tree nuts, the allergens most relevant to severe food allergy and anaphylaxis, occur in approximately 1 percent of children and adults. Severe whole-body allergic reactions, also known as anaphylaxis, are a frequent cause of emergency room visits, many of which are attributed to food allergy. Every year in the United States, it is estimated that there are approximately 15,000-30,000 episodes of food-induced anaphylaxis. NIH seeks to understand better both the immune system response to food allergies and how certain foods trigger an allergic reaction. Researchers in the United States and abroad are conducting clinical trials to improve management of allergy to cow's milk, egg, and peanut, and innovative clinical trials are assessing strategies to prevent development of peanut allergies. One important trial will determine whether early and regular consumption of a peanut snack by infants and very young children at risk of developing peanut allergy will promote tolerance and prevent the development of this allergy. In FY 2008, NIH sought to bring new investigators into the field through the Exploratory Investigations in Food Allergy initiative, which supports innovative pilot studies and developmental research on the mechanisms of food allergy. The program will be recompeted in FY 2010. During this period, NIH continued funding for the Consortium of Food Allergy Research, which supports basic, preclinical, and clinical research to assess the pathophysiology and natural history of food allergy-associated anaphylaxis and to develop interventions to prevent and treat food allergy.

- For more information, see <http://www3.niaid.nih.gov/topics/foodAllergy/default.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E/I) (NIAID)

Clinical and Translational Research

Muscle Recovery After Exercise or Injury: NIH funds a robust research portfolio on a wide range of basic, translational, and clinical research projects in skeletal muscle biology and diseases. In the past 2 years, NIH-funded scientists have published several papers on compounds that improve muscle function and endurance in animals. They hope that this new knowledge can be applied to improve treatments for certain muscle disorders, frailty, obesity, and other conditions in which exercise is known to be helpful, but not always practical. For example, researchers have identified two drugs that, in mice, seem to confer many of the healthful benefits of long-term exercise by giving the animals more fat-burning muscle and better endurance. Their discovery built on earlier, more basic research, which identified a protein that regulates several fat-burning genes in muscle cells. Other researchers, exploring the role of a protein found in immature muscle cells, discovered that creatine supplements taken by athletes play an important role in muscle repair. Elsewhere, at the University of Iowa's Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center, scientists have identified a disrupted molecular pathway that leads to fatigue after even mild physical exertion in mice with muscular dystrophy. Their study demonstrated that a signaling pathway that regulates blood vessel constriction in skeletal muscle after mild exercise is defective in mouse models for Duchenne muscular dystrophy and other myopathies. This finding may lead to treatments for the post-activity exhaustion that strikes many people who have neuromuscular disorders.

- Kobayashi YM, et al. *Nature* 2008;456(7221):511-5. PMID: 18953332. PMCID: PMC2588643.
- Narkar VA, et al. *Cell* 2008;134(3):405-15. PMID: 18674809. PMCID: PMC2706130.
- O'Connor RS, et al. *J Physiol* 2008;586(Pt 12):2841-53. PMID: 18420707. PMCID: PMC2517193.
- For more information, see http://www.nih.gov/news/research_matters/august2008/08112008mouse.htm
- For more information, see http://www.nih.gov/news/research_matters/november2008/11032008neuromuscular.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIAMS, NCRR, NIA, NICHD, NINDS) (COE)

Toward Better Treatment for Muscular Dystrophy: NIH is pursuing multiple pathways to therapeutic development for the muscular dystrophies. NIH funded two new Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers in FY 2008: the Boston Biomedical Research Institute, which seeks to identify biomarkers that can be used in preclinical studies and clinical trials of potential facioscapulohumeral muscular dystrophy (FSHD) therapies, and a center at the University of North Carolina at Chapel Hill, which is developing and testing gene therapies for Duchenne muscular dystrophy (DMD) and other muscle disorders. Collectively, the Wellstone centers program is designed to accelerate the translation of fundamental scientific advances to the clinic (see Chapter 4) and to serve as a national resource for the muscular dystrophy community through core facilities and training programs. NIH funds multiple approaches to therapeutic development through projects outside of the Wellstone program, including a robust portfolio on translational research in muscular dystrophy. Research currently is solicited in this area through two Funding Opportunity Announcements (FOAs) released in 2008: Exploratory/Developmental Projects for Translational Research in Neuromuscular Disease (R21) and the Cooperative Program in Translational Research in Neuromuscular Disease (U01). Previous FOAs on Translational Research in Muscular Dystrophy resulted in a number of funded projects in this area, including projects to develop small molecule drugs and to develop effective gene therapy design and delivery approaches. Progress also is being made toward the GPRA goal to "advance two emerging strategies for treating muscular dystrophy to clinical trial readiness by 2013."

- For more information, see <http://www.wellstonemdccenters.nih.gov/>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NINDS, NHLBI, NIAMS, NICHD) (COE, GPRA)

NIH Committee on the Science of Behavior Change (SOBC): A key national goal, at the scientific and policy level, is to eliminate preventable diseases and their associated disabilities and premature deaths. To achieve this goal, the science of behavior change increasingly is being recognized as a critical area for research. While NIH historically has invested in biobehavioral research, SOBC is a crucial step to coordinate, leverage, and advance these efforts. The SOBC initiative examines topics that span the continuum of behavior change and across disciplines. The SOBC goals include the identification of new and productive paradigms for SOBC research—paradigms that will facilitate the synthesis, integration, and application of SOBC research; that will help to bridge the distances that often separate investigators and disciplines; and that will inform and identify future research directions and initiatives. On June 15-16, 2009, NIH brought together experts in the fields of basic and applied behavioral sciences, genetics, economics, and methodology with the goal of advancing an NIH-wide agenda on the science of behavior change. The main topics of discussion were the acquisition and prevention of behavior, changing existing behavior, and maintenance of behavior. The SOBC working group will use ideas generated from the meeting to develop new interdisciplinary initiatives in behavior change research.

- For more information, see http://nihroadmap.nih.gov/documents/SOBC_Meeting_Summary_2009.pdf
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NINR, NIA, DPCPSI, FIC, NCCAM, NCI, NHGRI, NHLBI, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIGMS, NIMH, NINDS, OBSSR)

Rodent Model Resources for Translational Research: Mouse and rat models are the primary testbed for preclinical research and have played a vital role in most medical advances in the last century. Rodent models comprise about 90 percent of all animal studies, enabling a wide range of genetic and physiological research on human disease. NIH plays a major role in supporting the availability of normal and mutant mice and rats for translational research. Recent accomplishments include:

- *Knockout Mouse Project (KOMP)*—A trans-NIH initiative to individually inactivate approximately 8,500 protein-coding mouse genes to better understand their genetic functions, which are, in many cases, very similar to human genes. High throughput production started in 2006, and international distribution of validated embryonic stem cell lines with specific knockouts from the KOMP Repository became fully operational in 2008. The KOMP is supported by 19 ICs and Offices.
- *Mutant Mouse Regional Resource Centers*—More than 1,700 mutant mouse lines, and 27,000 mutant embryonic cell lines, are available from the consortium, which comprises three centers across the United States.
- *Rat Resource and Research Center*—Acquisition and distribution of rat models increased dramatically in FY 2008, because of adaptation of novel technologies to make directed mutations.

- For more information, see <http://www.genome.gov/17515708>
- For more information, see <http://komp.org>
- For more information, see <http://www.nih.gov/science/models/mouse/knockout/komp.html>
- For more information, see <http://www.mmrrc.org/>
- For more information, see <http://www.nrrrc.missouri.edu>
- For more information, see http://www.ncrr.nih.gov/comparative_medicine/resource_directory/rodents.asp
- This example also appears in Chapter 3: *Genomics*
- (E) (NCRR, NHGRI, NIDA, NINDS)

Biomedical Technology Research Centers (BTRCs): The BTRCs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Centers and through intensive collaborations with other leading laboratories. The BTRCs are used annually by nearly 5,000 scientists

Clinical and Translational Research

from across the United States and beyond, representing more than \$700 million of NIH funding from 22 ICs. As an example, optical technologies enable researchers to:

- Harness the power of light to "see" biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

→ For more information, see http://www.ncrr.nih.gov/biomedical_technology

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*

→ (E) (NCRR)

Glycomics Technology Development, Basic Research, and Translation into the Clinic: Glycans are ubiquitous complex carbohydrates found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules is thus critical for basic and clinical research across the spectrum of health and disease, but widely is regarded as one of the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- Biomedical Technology Research Centers develop and share cutting-edge technologies for analysis of carbohydrates in complex biological systems.
- Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.
- Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
- A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.

→ For more information, see <http://www.ncrr.nih.gov/glycomics>

→ For more information, see <http://www.functionalglycomics.org>

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*

→ (E) (NCRR, NCI, NHLBI, NIGMS, NINDS)

Translational Research at Primate Research Centers: Nonhuman primates are critical components for translational research because of their close physiological similarities to humans. Nonhuman primates widely are used for both hypothesis-based and applied research directly related to human health, such as the development and testing of vaccines and therapies. The NIH-supported National Primate Research Centers (NPRCs) and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using nonhuman primates. NIH support for the centers ensures that these specialized resources are available to the research community. Several NIH ICs provide funding to investigators for specific research projects that use NPRC resources, thus increasing the efficiency of projects involving use of nonhuman primates. For example, in FY 2008, more than 1,000 research projects and more than 2,000 investigators used the animals and other resources provided by the NPRCs. Highlights of research activities include:

- Use of the simian immunodeficiency virus for AIDS-related research, including development and testing of novel microbicides to prevent infection by HIV, the virus that causes AIDS, and testing of AIDS vaccine candidates.
- Identification of the central role of specific genes and molecules in drug addiction and neurological conditions and diseases, studies of the biochemistry and physiology of drug and alcohol addiction, and development of stem cell-based therapies for neurodegenerative diseases.
- Development of the first nonhuman primate model of a neurodegenerative disease-Huntington's disease.

→ Yang SH, et al. *Nature* 2008;452(7197):921-4. PMID: 18488016. PMCID: PMC2652570.

→ For more information, see http://www.ncrr.nih.gov/comparative_medicine/resource_directory/primates.asp

→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*

→ (E) (NCRRL, NIA, NINDS)

Challenge Program in Integrative Research: Mechanisms of Susceptibility to Oxidative-Stress Disease: This project is an interdisciplinary, collaborative effort to combine the use of simple eukaryotic systems, mouse models, genetic polymorphisms, genomics, clinical research, and patient samples to investigate the mechanisms of susceptibility to the development of oxidative stress-induced disease. The initial phase of the program is focused on bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP), chronic diseases associated with very low birth weight infants. This program consists of three interactive projects: (1) positional cloning of BPD/ROP susceptibility genes in inbred mice; (2) investigating the role of mitochondrial reactive oxygen species in hyperoxia-induced tissue injury; and (3) searching for oxidant susceptibility genes and neonatal diseases in prospective case-parent triad cohorts. Together this group will identify stress response networks, develop and validate early biomarkers of disease, and identify candidate genes and genetic polymorphisms that influence susceptibility to oxidative stress. This program has established a highly collaborative research team uniting bench science with clinical research and patient outcomes. The long-term goal of this program is to understand the role of specific genes that increase human susceptibility to oxidant stress-induced diseases. Thus, this team has the potential to affect a large number of environmentally induced diseases associated with inflammation and reactive oxygen species, including asthma, atherosclerosis, cancer, cardiovascular disorders, and neurodegenerative diseases.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*

→ (I) (NIEHS)

Stem Cells and Regenerative Medicine: Stem cells are able to renew themselves and generate progeny that differentiate into more specialized cells. They play critical roles in organism development, and some are essential for normal homeostasis and tissue repair. NIH has made a significant investment in stem cell research. One NIH-supported study showed that the sex of cells in a subpopulation of muscle-generating stem cells in adult mice can influence their capacity to repair tissue considerably. This finding could lead to future therapies for various diseases, including muscular dystrophy. A collaboration between NIH Intramural researchers and those at Walter Reed Army Medical Center discovered that waste tissues from surgery, removed to promote healing of orthopaedic injuries and war-traumatized muscle, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells. They could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest cells. NIH has partnered with the Department of Defense on an initiative to speed treatments to wounded soldiers abroad, and civilian trauma victims and burn patients in the United States. This collaboration has resulted in the establishment of the new Armed Forces Institute of Regenerative Medicine (AFIRM). The AFIRM-led program will focus on regrowing fingers, repairing shattered bones, and restoring skin to burn victims with genetically matched skin, to pave the way for commercial products in the near future. Hair follicles are useful models for organ regeneration. Recent discoveries have been made in the molecular processes that govern the growth of hair follicle stem cells, which are a source for newly formed hair follicles.

Clinical and Translational Research

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- Horsley V, et al. *Cell* 2008 Jan 25;132(2):299-310. PMID: 18243104. PMCID: PMC2546702.
- Nesti LJ, et al. *J Bone Joint Surg Am* 2008;90(11):2390-8. PMID: 18978407. PMCID: PMC2657299.
- For more information, see
http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cell_sex_and_stem_cell.asp
- For more information, see
http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/progenitor_cells.asp
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E/I) (NIAMS, NIA, NIAID, NIBIB)

Bisphenol A Exposure and Effects: More than 90 percent of the U.S. population is exposed to low levels of BPA. Exposures may occur through use of polycarbonate drinking bottles and the resins used to line food cans. The NIH National Toxicology Program's (NTP's) Center for the Evaluation of Risks to Human Reproduction conducted an evaluation to determine whether current levels of exposure to BPA present a hazard for human reproduction and/or development. Following this evaluation of existing literature, the NTP expressed "some concern" for effects on the brain, behavior, and prostate gland based on developmental effects reported in some laboratory animal studies using BPA exposures similar to those experienced by humans. NIH is working to address and support research and testing needs identified during the NTP evaluation to understand any potential risks for humans from BPA exposure. In collaboration with scientists at the FDA National Center for Toxicological Research, the NTP has designed and begun studies to evaluate similarities and differences in how rats metabolize BPA in relation to nonhuman primates, and to further understand the long-term health consequences from exposures to low levels of BPA during rodent development. In addition, NIH is providing grant support to the extramural community for studies that focus on investigating possible long-term health outcomes from developmental exposure or chronic exposures to environmentally relevant doses of BPA. Collectively, these studies should address research gaps, reduce uncertainties, and provide perspective regarding any potential risk that BPA poses for public health.

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- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
- (I) (NIEHS)

Experimental Therapeutics for Cancer: The NCI Experimental Therapeutics Program (NExT) is an integrated drug discovery and development effort that concentrates research into a single robust pipeline that starts with discovery of promising compounds and leads, through a series of progressive steps, to first-in-human studies. The ultimate goal is to accelerate the translation of new oncology agents to the clinic.

- For more information, see http://dctd.cancer.gov/About/major_initiatives_NExt.htm
- This example also appears in Chapter 2: *Cancer*
- (E/I) (NCI)

Alzheimer's Disease Neuroimaging Initiative (ADNI): ADNI is an innovative public-private partnership for examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease (AD). ADNI has reached its target enrollment of 800 participants, and supported development of a number of tools and methods now in use in the United States as well as in Japan, the European Union, and Australia. Other expansions include a genome-wide association study of ADNI participants scheduled to provide the most extensive and robust dataset of its kind in the AD field; a study that allows for longitudinal analysis by the collection of additional cerebrospinal fluid from participants over several years; and a study exploring the use of PET and Pittsburgh Compound B (PIB) as a tool for developing biochemical markers. A recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer's and established a method and standard of testing for these biomarkers.

- For more information, see <http://www.loni.ucla.edu/ADNI>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIA, NIBIB)

Therapeutics for Rare and Neglected Diseases Program (TRND): NIH is developing a congressionally mandated therapeutics development program for rare and neglected diseases. The ORDR will handle oversight and governance of TRND, and researchers will perform TRND's laboratory work in a new facility administered by the intramural program of NHGRI. TRND will build upon the similarly structured NIH Chemical Genomics Center (NCGC). NCGC facilitates drug development from the basic research laboratory to the chemical probe stage, which is when researchers begin to lay the groundwork for intensive preclinical development of candidate drugs. Picking up where NCGC and other organizations leave off, TRND will concentrate its efforts on the preclinical stage of drug development. TRND's aim will be to move candidate drugs forward in the drug development pipeline until they meet Food and Drug Administration (FDA) requirements for an Investigational New Drug (IND) application. Once TRND generates enough data to support an IND application for a candidate drug, it will be licensed to an experienced organization outside of NIH, such as a biotechnology or pharmaceutical company, for human testing and regulatory submission. TRND also will devote considerable resources to the repositioning or repurposing of approved products for use in rare and neglected diseases. Like NCGC, TRND will pull together researchers with expertise in a broad and diverse range of scientific disciplines and disease areas. Specifically, TRND will encourage investigators from both inside and outside of NIH, from the public, private, and nonprofit sectors, to submit projects for work within its intramural facility. This will create ongoing collaborations that will benefit researchers and, most importantly, patients with rare and neglected diseases. NIH ICs and Offices have recommended staff members with expertise and experiences in product development programs to serve on a Trans-NIH Staff Advisory Group that will provide ongoing consultation regarding the operation of TRND and help integrate TRND with related or complementary efforts in the NIH ICs. A second group providing input for TRND is the External Expert Panel comprised of experts in preclinical drug development and rare and neglected diseases from academia, industry, and patient advocacy communities.

Clinical and Translational Research

- For more information, see <http://www.genome.gov/27531965>
- For more information, see <https://rarediseases.info.nih.gov/TRND/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E/I) (**ODP/ORDR**, NHGRI)

Neurobiology of Pain in Sickle Cell Disease: The past 35 years have produced a remarkable expansion in scientific understanding of the neurobiological basis of pain, yet none of this research has been specifically focused on sickle cell disease (SCD), one of the few human diseases associated with lifelong, often severe, pain. To address this gap, an NIH-sponsored working group brought together researchers studying the neuroscience of pain and hematologists having a special interest in SCD. Participants identified an urgent need for multidisciplinary studies encompassing neurobiology, hematology, pharmacology, and psychology. Based on the working group findings, in November 2008, NIH issued a request for grant applications, Exploratory Studies in the Neurobiology of Pain in Sickle Cell Disease, to support basic and translational studies on the distinctive aspects of pain syndromes in SCD.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-008.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (**NHLBI**, NINDS)

NIH Guidelines on Ethical Issues Associated with Human Specimen and/or Data Collections: Human specimen and/or data collections increasingly are important for advancing basic biomedical and behavioral research and translating discoveries into improved health care. While numerous regulations and policies apply to specimen and data research, there is no comprehensive Federal policy that covers the full spectrum of activities involved with collection, storage, sharing, distribution, and use of human specimens and/or data for research. To address this need, NIH is developing draft guidelines for human specimen and data collections conducted or supported by NIH. The guidelines address ethical issues, including informed consent, protection from research risks, withdrawal of specimens and data, as well as management, oversight, access, and dissemination. The draft guidelines are expected to be issued for public comment in late 2009.

- For more information, see http://oba.od.nih.gov/policy/policy_issues.html#CRP_004
- (O) (**OSP/OBA**)

Molecular Profiling to Tailor Cancer Treatment: Molecular profiling is a powerful tool for identifying tumor subtypes and guiding clinical decisions to optimize patient benefit. NIH programs in this area include the Strategic Partnering to Evaluate Cancer Signatures (SPECS) Program, which is evaluating the clinical utility of molecular signatures and helping translate molecular data into improved patient management, and the Lymphoma/Leukemia Molecular Profiling Project. Several studies from these and other programs demonstrate the value of tailoring cancer treatment based on molecular characteristics of the patient and tumor. Gene expression profiling revealed distinct diffuse large B-cell lymphoma (DLBCL) subtypes, one of which exhibits activation of the pro-survival NF- κ B pathway. A recent study confirmed that bortezomib, a drug that indirectly prevents NF- κ B activation through proteasome inhibition, selectively enhances the effects of chemotherapy in this DLBCL subtype. A recent study revealed that head and neck squamous cell carcinomas (HNSCCs) associated with human papilloma virus (HPV)-16 are more responsive to treatment than HPV-negative HNSCCs. Results from a recent clinical trial indicate that advanced colorectal cancers should be tested for mutations in the KRAS gene. Patients with tumors housing KRAS mutations are unlikely to benefit from targeted therapies that block epidermal growth factor receptor activity and should thus be spared the side effects and costs associated with these drugs. SPECS researchers recently developed an assay to classify breast cancer molecular subtypes and showed that when used in combination with clinicopathologic parameters (e.g., stage, grade), the assay improved prediction of prognosis and chemotherapy benefit.

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- For more information, see <http://www.cancerdiagnosis.nci.nih.gov/specs/index.htm>
- For more information, see <http://lmpp.nih.gov>
- (E/I) (NCI)

Nanotechnology in Cancer: Nanotechnology innovation has been driven predominantly by physicists, engineers, and chemists; progress in cancer research comes primarily from discoveries of biologists and oncologists. The NIH Alliance for Nanotechnology in Cancer has set a goal of creating a community of cancer nanotechnologists who work together to develop nanotechnology approaches; apply them to the prevention, diagnosis, and treatment of cancer; and educate the medical community about opportunities enabled by cancer nanotechnology. The Alliance organized a session at 2009 American Association for Cancer Research meeting on Cancer Diagnostics Using Nanotechnology Platforms. Participants included high-profile investigators who work on the development of new nanodevices for in vitro diagnosis and in vivo imaging and clinicians who define oncology applications of those devices. Examples of this work include: PRINT, a technique allowing for controllable fabrication of nanoparticles; researching novel diagnostic techniques for proteins and DNA; developing implantable nanosensors; researching novel nanoparticle-based imaging agents and nanosensors; and developing nanotechnology-based cancer screening tools.

- For more information, see <http://nano.cancer.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*
- (E/I) (NCI)

NIH Bench-to-Bedside Program: An intramural Bench-to-Bedside Program was established in 1999 to integrate the work of basic and clinical scientists on the NIH campus and to foster collaborations across Institutes. Since the program's beginning, more than 500 principal and associate investigators have collaborated on 152 funded projects with approximately \$33 million distributed in total bench-to-bedside funding. The program scope broadened in 2006 to include partnerships between intramural and extramural programs as part of a broader NIH effort to reduce barriers between intramural and extramural communities. Four funding cycles have been completed successfully, with approximately 50 extramural institutions partnering on bench-to-bedside awards (15 of these are CTSA sites). Last year the program expanded to allow extramural investigators to initiate bench-to-bedside awards. The call for proposals invited extramural investigators to identify intramural partners to lead the study via the CTSA network. As NIH explores opportunities to promote expanded collaborations with extramural clinical researchers, governing entities are exploring stable funding for the Bench-to-Bedside Program. Also under consideration is the establishment of a grants-type mechanism for bench-to-bedside awards that would allow direct funding to intramural and extramural investigators and streamline funds distribution. This program has served as a successful model of an intramural initiative that has broadened to include extramural partnerships.

- For more information, see <http://clinicalcenter.nih.gov/cc/btb/awards.shtml>
- (E/I) (CC, NCMHD, NCRR, OAR, OBSSR, ODP/ORDR, ORWH)

Clinical Research: Learning Which Interventions Work

Recovery After an Initial Schizophrenic Episode (RAISE): Significant impairment of social and vocational function is the norm in chronic schizophrenia, and while antipsychotic drugs remain effective, they are not able to restore skills and abilities lost to the illness. A person experiencing an initial psychotic episode usually responds well to antipsychotics and, unlike chronically ill patients, may recover completely from that first episode. NIH will fund an initiative to determine

Clinical and Translational Research

whether function could be preserved and disability forestalled after an initial schizophrenic episode with an intense and sustained pharmacological, psychosocial, and rehabilitative intervention. A single project will be supported to: (1) test the feasibility of recruiting and retaining newly diagnosed patients in a longitudinal trial; (2) develop the treatment model—a mix of pharmacological, psychological, and rehabilitative interventions—that is most likely to preserve function and maintain patient participation; and (3) determine the nature of the control intervention. This initiative will set the stage for a large-scale, definitive, randomized clinical trial.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIMH) (ARRA)

Clinical Trials Networks for the Treatment of Mental Disorders: NIH is using its extensive clinical trials networks as platforms for investigating effective treatments for mental disorders. The networks, which are maintained through infrastructure supported by NIH, evolved from a recent series of practical clinical trials. The networks comprise more than 60 sites throughout the United States that maintain continual outreach efforts to diverse groups of patients and families with mental illnesses. The Bipolar Trials Network is conducting the Lithium Use for Bipolar Disorder (LiTMUS) trial, which will study the use of moderate-dose lithium for the treatment of bipolar disorder among 264 participants. The Depression Trials Network is seeking participants for the Combining Medications to Enhance Depression Outcomes (COMED) trial. This study will examine for the first time whether two different medications, when given in combination as the first treatment step, compared to one medication, will enhance remission rates, increase speed of remission, be tolerable to the participant, and provide better sustained benefits in the longer term. Results of this study, involving 660 participants, will inform practitioners in managing the treatment of patients with chronic or recurrent depression.

- For more information, see <http://www.clinicaltrials.gov/show/NCT00667745>
- For more information, see <http://www.clinicaltrials.gov/show/NCT00590863>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIMH)

Advances in Mental Health Treatment Development: NIH continues to fund research into the development of targeted medications and treatments for mental disorders.

- *Novel NeuroAIDS Therapies:* Integrated Preclinical/Clinical Program (IPCP): The IPCP supports drug development efforts focused on new targets that may modulate immune responses and protect brain cells in the context of HIV infection. One NIH-supported group will develop the use of nanotechnology to enhance delivery of HIV drugs to the brain. Another research group will investigate the therapeutic potential of various compounds to treat or prevent HIV-associated mental disorders.
- *Innovative Approaches to Personalizing the Treatment of Depression:* NIH will advance research on individualizing the treatment of depression by supporting efforts to develop models and test new approaches that, by accounting for patient characteristics, aim to be more specific and thus potentially lead to more effective and efficient treatment interventions. Several studies will be supported through this initiative.
- *Fast-acting Depression Treatments:* Previous NIH-funded research found that ketamine can lift depression in just hours, instead of the weeks it takes conventional antidepressants. NIH researchers now have identified a marker that predicts a patient's response using the split-second accuracy of magnetoencephalography. Depressed patients showed increased activity in the anterior cingulate cortex (ACC; a region found in brain imaging studies to signal better treatment responsiveness) that correlated with their response to ketamine while viewing certain visual stimuli. This ACC activity may indicate the dysfunctional workings of the brain circuit that is targeted by ketamine.

- Salvadore G, et al. *Biol Psychiatry* 2009;65(4):289-95. PMID: 18822408. PMCID: PMC2643469.
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-040.html>

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-010.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E/I) (NIMH)

Functional Gastrointestinal (GI) Disorders: NIH is leading a number of initiatives to improve the diagnosis and treatment of functional GI disorders. The Gastroparesis Clinical Research Consortium (GpCRC) performs clinical, epidemiological, and therapeutic research to improve treatment of patients with gastroparesis (inability to move food properly from the stomach through the digestive system). Ongoing GpCRC studies include the Gastroparesis Registry and a multicenter, randomized clinical trial testing the use of nortriptyline (a tricyclic antidepressant) for treatment of gastroparesis. The use of antidepressants for the treatment of functional dyspepsia (indigestion) is being tested in the Functional Dyspepsia Treatment Trial; the study also aims to identify genetic markers associated with improved treatment outcomes. Additional NIH-sponsored clinical studies are testing the benefit of short-term cognitive-behavioral treatment for irritable bowel syndrome (IBS) and evaluating methods for diagnosing and treating Sphincter of Oddi Dysfunction, a disorder that results in bouts of abdominal pain from spasms of biliary and pancreatic valves. In addition, NIH provides continued support for the Center for Neurovisceral Sciences and Women's Health at UCLA, which conducts basic and clinical research on how the brain and digestive system communicate and how alterations in this communication result in IBS and other disorders. These initiatives will reduce the physical and psychosocial burdens associated with functional GI disorders.

- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00398801>
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00765895>
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00248651>
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00738920>
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00688662>
- For more information, see <http://www.cns.med.ucla.edu>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDDK, NCCAM, ORWH)

Phase II Clinical Trials of Novel Therapies for Lung Diseases: Better treatments and diagnostic procedures are needed for lung diseases and sleep disorders. Although the results of basic research studies in cells, tissues, and animal models; investigations of biomarkers; and functional genomics have improved understanding of the pathogenesis of lung diseases and sleep disorders and suggested treatment targets, human testing often has not kept pace with the basic science advances. A recent solicitation encourages Phase II clinical trials to provide high-quality, proof-of-concept data to justify larger clinical efficacy trials. To foster collaborations between basic and clinical researchers and to obtain mechanistic understanding of new treatment approaches, each project is to include one interventional clinical trial led by a clinical investigator and at least one basic ancillary research study that is tightly related to the clinical question and led by a basic researcher. It is expected that four to six awards will be made in FYs 2010 and 2011.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-003.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NHLBI)

Obstructive Sleep Apnea Treatment Trials: In 2009, NIH completed two prospective, randomized, double-blinded, sham-controlled multicenter evaluations of nasal continuous positive airway pressure (CPAP) as a first-line treatment for obstructive sleep apnea (OSA). OSA is characterized by brief episodes of airway obstruction that prevents air from reaching the lung and disturbs sleep. It is the single most pervasive airway disorder and is associated with a greater risk of behavioral impairment, hypertension, stroke, diabetes, and all-cause mortality. The \$14 million Apnea Positive Pressure

Clinical and Translational Research

Long-Term Efficacy Study (APPLES) was launched in September 2002 to determine whether CPAP therapy, compared with placebo, alleviates debilitating cognitive impairment associated with OSA. More than 1,100 OSA cases were studied over a period of 6 months using a battery of behavioral and sleep tests to assess changes in cognitive ability, mood, sleepiness, and quality of life. The \$3 million CATNAP study was launched in August 2003 to assess the threshold of OSA severity at which CPAP therapy improves sleep-related functional and medical outcomes. It studied 200 cases of mild OSA in which participants exhibited significant sleepiness. Findings from APPLES and CATNAP that are to be reported in 2010 will be the first evidence from U.S.-based clinical trials to guide health care providers in determining who should be evaluated and treated and what behavioral benefits can be expected.

- Kushida CA, et al. *J Clin Sleep Med* 2006;2(3):288-300. PMID: 17561541.
- Saboisky JP, *Expert Opin Ther Targets* 2009;13(7):795-809. PMID: 19530985. PMCID: PMC2729816.
- Calvin AD, et al. *Metab Syndr Relat Disord.* 2009;7(4):271-8. PMID: 19344228.
- For more information, see <https://apples.stanford.edu>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NHLBI)

The Osteoarthritis Initiative: A limited number of therapies exist for osteoarthritis (OA) treatment. Most only relieve pain and reduce disability; none slows or halts disease progression. One barrier to the development of drugs that block the underlying causes of OA symptoms is the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. To overcome this problem, NIH—with input from FDA—partnered with private sponsors to create the Osteoarthritis Initiative (OAI). When complete, the OAI will provide an unparalleled state-of-the-art database showing both the natural progression of the disease and information on risk factors, joint changes, and outcome measures. All data will be freely available to researchers worldwide, who can develop hypotheses about possible OA biomarkers of disease onset and progression, test their theories, describe the natural history of OA, and investigate factors that influence disease development and severity. Scientists also can use the OAI to identify potential disease targets and to develop tools for measuring clinically meaningful improvements. The OAI originally was to receive funding through FY 2009, during which time investigators would collect survey, clinical, and image data and biological samples from approximately 4,800 people at baseline, 12-, 24-, 36-, and 48-month time points. NIH extended the study to include 72- and 96-month data. By the end of FY 2009, more than 1,350 researchers from 54 countries had registered to access OAI data. A total of 4,100 clinical datasets have been downloaded. In FYs 2008 and 2009, more than 18 articles using OAI data were accepted for publication in peer-reviewed journals.

- For more information, see http://www.niams.nih.gov/Funding/Funded_Research/Osteoarthritis_Initiative
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIAMS, NCCAM, NCMHD, NIA, NIBIB, NIDCR, ORWH) (GPRA)

Progress Toward Immune Tolerance: Since 1999, NIH, with its cosponsor the Juvenile Diabetes Research Foundation International, has supported the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. The ITN is pioneering novel strategies for studying and testing new drugs and therapies against autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based upon principles of immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to "reeducate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. To understand the underlying mechanisms of action of the candidate therapies and to monitor tolerance, the ITN has established state-of-the-art core laboratory facilities to conduct integrated mechanistic studies, and to develop and evaluate markers and assays to measure the induction, maintenance, and loss of tolerance in humans. Current ITN studies include pancreatic islet transplantation for type 1 diabetes; approaches to slow or reverse progression of autoimmune diseases such as type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus and other rheumatologic disorders; approaches to

treat and prevent asthma and allergic disorders, including food allergy; and therapies to prevent liver and kidney transplant rejection without using lifelong immunosuppressive drugs.

- For more information, see <http://www.immunetolerance.org/>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIAID, NIDDK)

Transforming TB Research: Diagnosis, treatment, and control of tuberculosis (TB) increasingly are complicated by the HIV/AIDS co-epidemic and the emergence of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR TB). NIH is pursuing six critical areas for additional investigation: (1) new TB diagnostic tools; (2) improved therapies for all forms of TB; (3) basic biology and immunology of TB; (4) MDR TB and XDR TB epidemiology; (5) clinical management of MDR TB and XDR TB in people with and without HIV infection, including children; and (6) TB prevention, including vaccines. Recent NIH advances in TB research include:

- Two FDA-approved drugs are found to work in tandem to kill laboratory models of *Mycobacterium tuberculosis* (Mtb) strains, the bacterium that causes TB. The drugs—meropenem and clavulanate—are used to treat other bacterial diseases. A clinical trial is being developed to test the combination in people who have XDR TB.
- New information on the pharmacology of existing and new anti-TB compounds may facilitate the development of improved treatment regimens for adults and children.
- Clinical trials have shown that the immune systems of children who are HIV-infected do not respond well to the current TB vaccine, BCG.
- Clinical trials also have shown that mortality among TB patients coinfecting with HIV is reduced drastically when antiretroviral therapy is provided at the same time as TB therapy. Additional studies are underway to determine optimal strategies for the prevention, treatment, and diagnosis of TB in the setting of HIV infection.

Several NIH-supported academic institutions, public-private partnerships, and commercial entities are developing rapid tests for early detection of all forms of TB, including MDR and XDR TB.

- For more information, see <http://www3.niaid.nih.gov/topics/tuberculosis>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E/I) (NIAID)

Preventing Drug Abuse in Children and Adolescents: Intervening early to reduce risk factors for drug abuse and related problem behaviors can have tremendous impact and improve the trajectory of a young life. NIH is using a multipronged approach to achieve more effective substance abuse prevention by: (1) developing novel strategies, (2) exploring long-term and crossover effects of proven programs, and (3) improving adoption and implementation of evidence-based approaches. Innovative ideas being explored include physical activity to counter drug use, interactive Web-based technologies to engage young people, and brain imaging results to better target media messages. NIH also is building on proven methods such as universal prevention programs, which can reduce an array of risk behaviors, including substance abuse. These programs typically target behaviors appropriate to a child's developmental stage and have been shown to achieve long-term effects. For example, fifth graders who participated in the school-based prevention program "Positive Action" as first graders were about half as likely to engage in substance abuse, violent behavior, or sexual activity as those who did not. Similarly, exposure to the "Good Behavior Game," designed to reduce aggressive, disruptive behavior in first and second grade classrooms, led to fewer drug and alcohol disorders, lower rates of regular smoking, less antisocial personality disorder, and reduced delinquency and violent crime in young adults. However, the development of evidence-based prevention programs is meaningless unless they are adopted by communities. Therefore, NIH also is striving to increase implementation of successful prevention approaches in U.S. schools and communities.

Clinical and Translational Research

- Beets MW, et al. *Am J Public Health* 2009;99(8):1-8. PMID: 19542037.
- Kellam SG, et al. *Drug Alcohol Depend* 2008;95 Suppl 1:S5-S28. PMID: 18343607. PMCID: PMC2512256.
- Spoth R, et al. *Am J Prev Med* 2007;32 (5):395-402. PMID: 17478265.
- For more information, see <http://www.nida.nih.gov/scienceofaddiction/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDA)

Comorbidity: Addiction and Other Mental Disorders: Drug addiction frequently is accompanied by other psychiatric diseases, which can complicate its diagnosis and treatment. Thus, NIH supports research on the multiple facets of psychiatric comorbidity across multiple health sectors. This approach explores whether drug use leads to mental illness or the reverse, what causes their frequent co-occurrence (e.g., shared genetic and environmental vulnerabilities or similarities in brain circuits and chemical messengers), and how to treat both comprehensively. Specific activities include epidemiological research on mental health/drug abuse comorbidity, such as secondary analyses of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study and the National Comorbidity Survey to better understand the prevalence and variety of comorbidities, and clinical trials to help assess the actions of combined or dually effective behavioral and medication treatments (e.g., in adolescent and adult patients with attention deficit/hyperactivity disorder [ADHD] and substance abuse problems). It also includes a push for research to investigate drug abuse and mental health screening for all those entering the criminal justice system, a notable gap, particularly for adolescents. Another identified gap calls for research using preclinical models of comorbidity to explore the neurological bases of comorbid drug abuse and other mental illness (e.g., overlapping circuitry). Joint requests for applications issued by multiple ICs have elicited studies examining everything from the role of depression and anxiety in the tobacco epidemic to the neural bases of ADHD in fetal drug or alcohol exposure to improving care for co-occurring disorders in rural areas via new technologies. (Note: NESARC and the National Comorbidity Survey are nationally representative surveys in the United States that assess the prevalences and correlates of DSM-III-R disorders, including substance use and mental health disorders.)

- For more information, see <http://www.drugabuse.gov/CTN/protocol/0028.html>
- For more information, see <http://www.drugabuse.gov/CTN/protocol/0029.html>
- For more information, see <http://www.nida.nih.gov/ResearchReports/comorbidity>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDA, NIAAA, NIMH)

The Critical Need for Addiction Medications: Breakthrough discoveries in the last decade have led to a profound transformation in understanding the mechanisms and consequences of drug abuse and addiction. The current picture offers a unique opportunity for the results of NIH's collective research to be translated into new, effective pharmacotherapies that could, either by themselves or with tested behavioral treatments, help alleviate the devastating personal and societal impacts of addiction. Distinct from the process that occurs with many other diseases, medications development for addiction suffers from minimal pharmaceutical industry involvement—likely because of real or perceived financial disincentives and stigma. Thus, despite many enticing scientific leads, we still have no medications available for stimulant, cannabis, inhalants, or polysubstance abuse, a gap that NIH is attempting to fill. Current efforts are capitalizing on a greater understanding of the neurobiology underlying addiction and of newly identified candidate systems and molecules. Several innovative treatment approaches—beyond targeting the brain's reward system—have proven feasible and are progressing to more advanced stages of research and development. Projects in this context include work on medications to diminish conditioned responses, promote new learning, and inhibit stress-induced relapse. In addition, vaccines (e.g., for nicotine, cocaine) are being developed that induce the body to produce drug-specific antibodies able to sequester drug molecules while they are still in the bloodstream and prevent them from entering the brain. Next-generation

pharmaceuticals also will emerge from human genome studies uncovering novel targets for better tailoring of treatments according to a person's genes.

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDA) (GPRA)

Comparative Effectiveness of Treatments for Common Childhood Eye Disorder: Convergence insufficiency (CI) is a relatively common vision problem that develops in childhood in which the eyes do not naturally turn inward when focusing on a close-up visual target. Symptoms include eye strain, blurred vision, headaches, and discomfort. CI can adversely affect reading ability and reading comprehension and can have a serious impact on an individual's performance in school, career, and quality of life. Eye care professionals treat CI with various forms of eye exercises, done at home or in the office of a trained therapist, that require children to sustain focus on nearby objects. The Convergence Insufficiency Treatment Trial (CITT) compared the effectiveness of these therapies. Results indicate that the most popular treatment, known as home-based pencil push-up therapy, was no more effective in improving patient's symptoms than a placebo therapy. However, 73 percent of children assigned to a regimen of intensive, office-based therapy combined with home reinforcement did improve significantly compared to the placebo group. Other commonly prescribed home-based regimens also showed some benefit but were only about half as successful as office-based therapy with home reinforcement. Although home-based treatments for CI are appealing because of their simplicity and low cost, these results indicate that office-based treatment combined with home reinforcement is more effective in helping children to achieve normal vision and reducing symptoms.

- Convergence Insufficiency Treatment Trial Study Group. *Arch Ophthalmol* 2008;126(10):1336-49. PMID: 18852411. PMCID: PMC2779032.
- For more information, see <http://archophth.ama-assn.org/cgi/content/full/126/10/1336>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NEI)

NIH Establishes Neuro-Ophthalmology Clinical Research Network: The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) Network was established in spring of 2009 to investigate disorders that bridge neurology and ophthalmology and that often are difficult to diagnose and treat. The Network involves more than 200 community and academic practitioners. This consortium will provide a unique opportunity to recruit and study hard-to-find patients to evaluate risks, diagnoses, and treatment options that could not be accomplished without a coordinated effort. The first clinical trial funded under this network will be the Idiopathic Intracranial Hypertension (IIH) Treatment Trial. IIH typically occurs in women of childbearing age. Obesity increases the risk 20-fold. IIH is characterized by an increase in intracranial pressure resulting in blurred vision, double vision, and permanent vision loss. This trial will compare the additional benefit of acetazolamide (a diuretic) added to a low-sodium, weight reduction diet in newly diagnosed patients. Future planned studies include comparing treatments for ocular manifestations in Graves' disease, an autoimmune disorder that causes hyperthyroidism, estimated to affect 2 percent of all women between the ages of 20 and 40. Patients with Graves' can develop protrusion of the eye balls and optic nerve damage. A network of researchers provides valuable expertise and widespread recruitment capabilities for studies of rare disorders.

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NEI)

Clinical and Translational Research

Comparative Effectiveness Study Finds Laser Treatment Preferable in Diabetic Macular Edema: The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network dedicated to conducting multicenter clinical research for diabetic retinopathy and associated conditions. The DRCR.net was formed in September 2002 and currently includes 199 participating sites with more than 670 physicians throughout the United States. About 45 percent of the 18 million Americans diagnosed with diabetes have visual disorders such as macular edema. This occurs when the central part of the retina called the macula swells in diabetics—possibly leading to blindness. Laser treatment to reduce swelling has been the standard of care. However, early reports of success in treating diabetic macular edema with a corticosteroid, triamcinolone, have led to its widespread use. A DRCR clinical trial found that laser therapy is more effective and has far fewer side effects than intraocular injections of triamcinolone in treating diabetic macular edema. In the corticosteroid-treated group, 28 percent experienced substantial vision loss as compared to 19 percent in the laser-treated group. Surprisingly and unexpectedly, vision improved in about one-third of the eyes treated with laser therapy. Results of this study confirm the preferential use of laser treatment for diabetic macular edema.

- Diabetic Retinopathy Clinical Research Network, et al. *Ophthalmology* 2007;114(10):1860-7. PMID: 17698196. PMCID: PMC2245885.
- For more information, see <http://public.drcr.net/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NEI)

Progress in Parkinson's Disease Research: For the past 7 years, NIH actively has been engaged in identifying gaps in Parkinson's disease research and developing programs to address them. Examples of progress include initiation of Phase III clinical trials of creatine and coenzyme Q10 to treat early Parkinson's disease; development of diagnostic criteria for depression and psychosis in people with Parkinson's disease; and support for a Parkinson's disease Gene Therapy Study Group. In 2009, a major clinical trial cofunded by NIH and the Veterans Administration published its finding that Deep Brain Stimulation is more effective than standard drug therapy for Parkinson's disease but also carries a higher risk of adverse events. NIH also has begun to formally assess the effectiveness of its programs by completing an evaluation of its Morris K. Udall Centers of Excellence in Parkinson's Disease Research. This evaluation included an assessment of scientific progress made by the centers and the value of using a centers mechanism, as well as an exploration of the effectiveness of program management and review in supporting the centers. The Working Group tasked with this evaluation released its findings in September 2007.

- Weaver FM, et al. *JAMA* 2009;301(1):63-73. PMID: 19126811.
- For more information, see <http://www.ninds.nih.gov/funding/research/parkinsonsweb/index.htm>
- For more information, see <http://www.parkinsontrial.ninds.nih.gov/index.htm>
- For more information, see http://www.ninds.nih.gov/news_and_events/press_releases/pressrelease_creatine_03222007.htm
- For more information, see http://www.ninds.nih.gov/udall_centers_evaluation
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NINDS)

Clinical Research and Trials in Neurological Disease: NINDS funds more than 1,000 extramural clinical research studies. Clinical researchers are studying, for example, disease mechanisms, risk factors that contribute to health disparities, brain imaging, and genes that predispose to disease as well as conducting multisite clinical trials that test the safety and efficacy of new prevention strategies and treatments or compare existing interventions. In the past year, for example, an NICHD/NINDS clinical trial reported that a drug commonly used to delay labor can prevent cerebral palsy in some circumstances, and a Veterans Administration/NINDS trial demonstrated that deep brain stimulation, a surgical intervention, is more effective than drug treatment at improving movement and quality of life for many people who have Parkinson's disease, but carries some risks. Among trials now underway, researchers are testing interventions to protect the

brain following traumatic brain injury, to prevent stroke, to slow the progression of neurodegenerative diseases, and to treat multiple sclerosis. An independent study contracted by NINDS found that NINDS clinical trials which cost \$335 million over 10 years provided benefits that exceeded \$15 billion and added 470,000 healthy years of life to people in the United States. With guidance from an expert strategic planning panel, NINDS is continuing to improve the efficiency and payoff of the clinical trials program.

- Johnston SC, et al. *Lancet* 2006;367:1319-27. PMID: 16631910.
- Weaver FM, et al. *JAMA* 2009;301(1):63-73. PMID: 19126811.
- Rouse DJ, et al. *N Engl J Med* 2008;359(9):895-905. PMID: 18753646.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NINDS, NICHD)

Research on Rare Neurological Disorders: NIH supports research to uncover the causes of and develop treatments for the hundreds of rare disorders that affect the nervous system, while also promoting research on topics such as stem cells, gene therapy, and neuroimaging that will impact multiple rare disorders. NIH reissued a Funding Opportunity Announcement (FOA) for new and renewal applications to continue the Rare Diseases Clinical Research Network (RDCRN), which funds collaborative clinical research consortia focused on rare diseases. NINDS will oversee the network's Data Management and Coordinating Center, and several of the consortia to be funded through this program focus on neurological disorders, including dystonia, brain vascular malformations, lysosomal storage disorders, and rare diseases of the autonomic nervous system. Through the NINDS translational research program, NIH supports milestone-driven therapy development for rare neurological diseases. Two funded projects, in Batten disease and Niemann-Pick disease, are nearing investigational new drug approval from FDA to conduct clinical trials, and a newly awarded project focuses on gene therapy approaches for the lysosomal storage disorders Tay-Sachs, San Filippo, and Sandhoff disease. NIH also continues to support and encourage research to understand and treat Ataxia-telangiectasia and dystonia (including rare dystonias) through separate FOAs issued in collaboration with patient organizations.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-272.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-397.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-08-001.html>
- For more information, see http://www.ninds.nih.gov/research/translational/Coop_Trans_Res.htm
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NINDS, NCI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NICHD, NIDCD, NIDCR, NIDDK, NIEHS, NINR, ODP/ORDR)

Specialized Program of Translational Research in Acute Stroke (SPOTRIAS): The objective of the SPOTRIAS is to serve as an incubator for translational and early-phase clinical research studies. SPOTRIAS sites are located at medical centers where staff have the capacity to evaluate and treat stroke patients very rapidly after symptom onset. NIH supports eight SPOTRIAS sites that have made substantial progress, including impressive increases in tPA use; the establishment of three interlinked repositories for protein and DNA tissue samples, neuroimages, and clinical data; enrollment of more than 951 individuals with acute stroke into treatment protocols; the management of 20 early-phase clinical trials; and the training of 79 research fellows.

- For more information, see <http://www.spotrias.com>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E, I) (NINDS)

Clinical and Translational Research

Clarification of Optimal Anticoagulation Through Genetics (COAG): NIH has launched the COAG trial to gain a better understanding of the influences of clinical and genetic characteristics of patients in determining a safe and optimal dose of the drug warfarin. The most commonly used oral anticoagulant in the United States, warfarin is used to prevent dangerous blood clots that can potentially lead to pulmonary emboli and strokes. The drug is challenging for doctors to prescribe because the ideal dosage can vary widely from one person to another. Getting the wrong amount of warfarin can be dangerous—if the dose is too high, patients could bleed profusely; if too low, life-threatening clots could develop. The COAG study will determine whether knowledge about some specific genes will help physicians find the safest, most effective warfarin dose for their patients. The prospective, multicenter, randomized clinical trial will recruit more than 1,200 patients who are beginning warfarin treatment. The knowledge gained in COAG will make significant scientific contributions to several medical specialties as well as the field of pharmacogenetics and personalized medicine.

- For more information, see <http://www.clinicaltrials.gov/ct2/show/NCT00839657>
- For more information, see <http://coagstudy.org>
- (E) (NHLBI) (GPRA)

Multiple Sclerosis Research: Although the exact cause of multiple sclerosis (MS) is unknown, recent research supported by NIH has begun to identify genetic variations associated with increased risk for developing the disease. In 2007, a genome-wide association study with NIH support reported the first new genetic risk factors for MS to be identified in more than 20 years, and in 2009, meta-analyses and replication studies revealed additional new susceptibility genes. NIH also funds and conducts basic, translational, and clinical research on disease mechanisms, biomarkers, and treatments for MS. For example, NIH supports a randomized, double-blind, placebo-controlled Phase III trial (CombiRx) comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting MS. The trial will determine whether combination therapy offers an improvement over the partial efficacy of either single treatment; it is the only direct comparison of these commonly used medications that is fully blinded and not supported by a commercial entity. NIH's Intramural Neuroimmunology Branch is collaborating with this trial to identify biomarkers associated with different clinical and treatment response profiles (BioMS). Such biomarkers may inform predictions about which treatment will most likely benefit a given patient, making this ancillary study an exciting addition to comparative effectiveness research in MS. Intramural investigators also will collaborate with the Swiss pharmaceutical company Santhera in a Phase I/II clinical trial to test the safety and efficacy of idebenone, which may protect against tissue damage, as a potential treatment for primary progressive MS.

- De Jager PL, et al. *Nat Genet* 2009;41(7):776-82. PMID: 19525953. PMCID: PMC2757648.
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00211887>
- For more information, see <http://clinicaltrials.gov/ct2/show/NCT00325988>
- For more information, see <http://clinicaltrials.gov/ct2/show/study/NCT00950248>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Autoimmune Diseases*
- (E, I) (NINDS)

Studies of Diabetes in Youth: NIH and CDC support the SEARCH for Diabetes in Youth study, which is providing key data on childhood diabetes incidence and prevalence. Recent data from SEARCH revealed unexpectedly high rates of diabetes in youth across most ethnic and racial groups in the United States. SEARCH also estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. To address the emerging problem of type 2 diabetes in youth, NIH supports the HEALTHY multicenter study to prevent risk factors for type 2 diabetes in middle-school children. A pilot study for HEALTHY found that an alarmingly high 15 percent of students in middle schools enrolling mainly minority youth had 3 major risk factors for type 2 diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease risk for obesity and diabetes. Thus, NIH launched the HEALTHY study in 2006. Half of the 42 participating middle schools receive the intervention, which includes changes to

school food service and physical education classes, behavior change, and communications campaigns. More than 70 percent of the enrolled students are from minority populations. For children who already have been diagnosed with type 2 diabetes, NIH supports the Treatment Options for Type 2 Diabetes in Youth (TODAY) study, which is comparing three different treatment strategies for children with the disease.

- Mayer-Davis EJ, et al. *Diabetes Care* 2009;32 Suppl 2:S99-101. PMID: 19246580. PMCID: PMC2647691.
- For more information, see <http://www.searchfordiabetes.org/>
- For more information, see <http://www.todaystudy.org/index.cgi>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDDK, CDC)

Preclinical and Clinical Research on Type 1 Diabetes: NIH's Type 1 Diabetes TrialNet is an international network that tests strategies for prevention and early treatment of type 1 diabetes. TrialNet recently found that the drug rituximab delayed progression of type 1 diabetes in newly diagnosed patients. To identify environmental triggers of type 1 diabetes, NIH established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium. TEDDY is enrolling newborns at high genetic risk and following them until age 15 to identify environmental triggers. NIH's landmark Diabetes Control and Complications Trial (DCCT) demonstrated that intensive control of blood glucose levels reduced complications of the eyes, nerves, and kidneys in type 1 diabetes patients. Long-term findings from the follow-on Epidemiology of Diabetes Interventions and Complications (EDIC) study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients begin intensive therapy as early as possible. To help patients achieve good glucose control, new initiatives focus on clinical and behavioral research related to new technologies for glucose control and insulin delivery (e.g., artificial pancreas technologies). NIH also supports research on islet transplantation through the Clinical Islet Transplantation Consortium. To provide resources for preclinical development of agents to test in clinical trials, NIH established the Type 1 Diabetes—Rapid Access to Intervention Development program.

- Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group, et al. *Arch Intern Med* 2009;169(14):1307-16. PMID: 19636033. PMCID: PMC2866072.
- Pescovitz MD, et al. *N Engl J Med* 2009;361(22):2143-52. PMID: 19940299.
- For more information, see <http://www.diabetestrialnet.org>
- For more information, see <http://www.teddystudy.org>
- For more information, see <http://diabetes.niddk.nih.gov/dm/pubs/control/>
- For more information, see <http://www.citissetstudy.org/>
- For more information, see <http://www.t1diabetes.nih.gov/T1D-RAID/>
- This example also appears in Chapter 2: *Autoimmune Diseases*
- (E) (NIDDK, NCCAM, NCI, NIAID, NICHD)

Obesity, Inflammation, and Fat Cell Biology: NIH supports diverse research on fat (adipose) tissue, including studies that examine the relationship between obesity and inflammation in white adipose tissue, as well as research on another type of fat tissue, brown fat. In obese patients, lipid laden white adipose tissue secretes a number of proinflammatory molecules such as TNF-alpha (as well as other types of signaling molecules associated with insulin resistance). Chronic low-grade tissue inflammation observed in obese individuals has been linked to type 2 diabetes and cardiovascular disease risk. An NIH-funded, multicenter research study called Targeting INflammation using SALsalate for Type-2 Diabetes (TINSAL-T2D) has been initiated to determine whether salsalate, an inexpensive anti-inflammatory drug, could be a new treatment option for patients with type 2 diabetes. A different avenue of research led to the surprising discovery of metabolically active brown adipose tissue in adult humans. While white fat cells store fat, brown fat cells burn fat to

Clinical and Translational Research

generate heat, and were once thought to exist only in infants. Research on brown fat in adult humans, as well as studies in animal models, may lead to novel strategies for obesity therapy.

- Cypess AM, et al. *N Engl J Med* 2009;360(15):1509-17. PMID: 19357406. PMCID: PMC1986615.
- Tseng YH, et al. *Nature* 2008;454(7207):1000-4. PMID: 18719589. PMCID: PMC2745972.
- Seale P, et al. *Nature* 2008;454(7207):961-7. PMID: 18719582. PMCID: PMC2583329.
- For more information, see <http://tinsalt2d.org/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDDK)

Look AHEAD (Action for Health in Diabetes): This NIH-led, multicenter, randomized clinical trial is examining the long-term health effects of an intensive lifestyle intervention (ILI) designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity. The study enrolled more than 5,100 overweight or obese adults with type 2 diabetes. Results from the first year of the study showed that participants in the ILI group achieved clinically significant weight loss; this was the case across all subgroups of the ethnically and demographically diverse study population. In addition, this weight loss was associated with an increase in "health-related quality of life" and improved cardiovascular fitness, blood pressure, cholesterol, and blood glucose, as compared to a control group receiving diabetes support and education. As another major point for health outcome measurement, the study recently completed 4 years of intervention and follow-up. In the coming years, continued follow-up of the Look AHEAD participants will show whether the ILI can reduce the incidence of heart attack and stroke and improve other health-related outcomes in this population. These findings will have important implications for treating type 2 diabetes.

- For more information, see <http://www2.niddk.nih.gov/Research/ClinicalResearch/ClinicalTrials/Patients/ClinicalResearchLookahead.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
- (E/I) (NIDDK, CDC, NCMHD, NHLBI, NINR, ORWH) (GPRA)

Behavioral Strategies to Improve Quality of Life and Chronic Disease Outcomes: While health care advances continue to transform previously acute/fatal conditions into chronic conditions and individual life expectancy is increasing, issues of quality of life have become ever more important. Studies focusing on the management of disease- and treatment-related symptoms have demonstrated the capacity for behavioral strategies to mitigate effects of symptoms and contribute to improving short- and long-term patient outcomes. For example, behavioral strategies have been shown to improve patient outcomes across various diseases including diabetes, irritable bowel syndrome, and asthma. In recognition of the need for new behavioral strategies to manage chronic illness, NIH has established a goal of developing and testing behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes by 2012. Beginning in FY 2008, progress toward achieving this goal has been updated annually in the Online Performance Index section of NIH's portion of the President's budget submission to Congress.

- For more information, see <http://officeofbudget.od.nih.gov/br.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NINR, NCI) (GPRA)

Developing Interventions to Improve Palliative Care at the End of Life: The life expectancy of the American people has reached a historic high, but along with increased life expectancy comes an increase in the number of people living with, and dying from, chronic debilitating diseases. Prolonged courses of decline at the end of life, palliative treatment options, and life-sustaining technologies have raised many important research questions within the last decade. In addition, the needs of dying children and their families are coming into greater focus, because death in childhood stands out as a

particular tragedy and a unique end-of-life experience for all involved. To address these needs, NIH-supported end-of-life science seeks to understand dying with respect to the needs of dying persons and formal and informal caregivers. It includes research on issues such as: alleviation of symptoms, psychological care, near-death preferences, advance directives, and family decision-making. Likewise, end-of-life research addresses the cultural, spiritual, age-specific, and disease-specific factors that make each person's experience at the end of life unique. In FY 2009, NIH announced a funding initiative to develop and test interventions to enhance end-of-life and palliative care that providers can implement across multiple settings, illnesses, and cultural contexts. NIH made the first awards under this solicitation in late FY 2009.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-09-004.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NINR, NCI)

Intervention Reduces Risky Sexual Behavior Among Homeless HIV-Infected Adults: HIV infection in the United States is found more commonly among populations with significant life stressors, such as homelessness and drug use. An NIH-funded program (the Healthy Living Program) already shown to reduce risky sexual and substance abuse behavior among HIV-infected adults also appears to be effective in improving the lives of HIV-infected homeless or near-homeless adults. The program consisted of three intervention modules of five sessions each, designed to help participants reduce risky sexual behaviors and drug use, improve their quality of life, and sustain healthy behaviors. Compared with a control group who did not receive the Healthy Living Program intervention, individuals who were homeless or near-homeless in the 3 years prior to and during the study and who participated in the intervention engaged in 34 percent fewer risky sexual acts and 72 percent fewer sexual encounters with partners who were not infected with HIV or were of unknown HIV status. The study's results highlight the importance of programs designed to prevent or reduce the spread of HIV among people in high-risk populations. They also indicate that intervention programs focusing on skills development and including the physical and mental health needs of participants, are more likely to succeed than programs focusing only on reducing HIV transmission.

- Rotheram-Borus MJ, et al. *Am J Public Health* 2009;99(6):1100-7. PMID: 18799777. PMCID: 2679793.
- For more information, see <http://www.nimh.nih.gov/science-news/2008/intervention-helps-reduce-risky-sexual-behavior-among-homeless-hiv-positive-adults.shtml>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIMH)

Research Initiatives to Study Suicidality and Mental Health Needs of U.S. Army Soldiers and Returning Combat Veterans: The high rates of mental health and behavioral adjustment problems among recent U.S. military combat veterans, and the increasing rates of suicide among Army soldiers, are of growing concern. To address these issues, NIH is collaborating with the U.S. Army to evaluate selected groups of soldiers across all phases of Army service, including entry-level training and service, pre-deployment training, deployment and noncombat assignments, post-deployment, and post-separation reintegration to civilian life. The study's intent is to identify modifiable risk and protective factors, as well as moderators, of suicide-related behaviors. NIH also is launching a study of the impact of existing national, state, and local community-based programs addressing the adjustment and mental health needs of recent combat veterans, including returning National Guard, Army Reserve, and newly separated active duty personnel. This initiative will produce new information concerning effective strategies for fostering successful transition from combat to civilian roles for returning service members.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-140.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-070.html>

Clinical and Translational Research

- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIMH)

Unexpectedly, Corneas from Older Donors Found Suitable for Transplantation: Light first enters the eye through the crystal clear cornea and is focused on the retina. Each year approximately 33,000 Americans undergo corneal transplants to replace diseased corneas that either become cloudy or no longer properly focus light, causing severe visual impairment. Corneal transplants are among the most common and successful transplantation procedures in medicine. Availability of donor tissue is key to this sight-restoring procedure. However, many eye banks refrain from harvesting tissue from donors over age 65 because of uncertainty about the integrity of older corneas. Newly instituted FDA regulations to further safeguard transplant recipients and the common use of LASIK surgery to correct refractive errors—which renders corneal tissue unusable for transplantation—could significantly limit future tissue supplies. The Cornea Donor Study (CDS) found that corneal transplants using tissue from donors ages 66-75 have similar success rates to those using tissue from donors ages 12-65. Based on these findings, the study authors recommend that the age limit for donor tissue could be safely expanded to age 75. The CDS study gives eye banks, transplant surgeons, and patients confidence in the use of older donor tissue, and should help eye banks keep pace with the demand for corneal tissue.

- Cornea Donor Study Investigator Group, et al. *Ophthalmology* 2008;115(4):620-626.e6. PMID: 18387407.
- For more information, see <http://www.ophsource.org/periodicals/ophta/article/PIIS0161642008000055/fulltext>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NEI)

Evidence-Based Review Program: In FY 2001, NIH received a congressional mandate to review the current scientific evidence on the efficacy and safety of dietary supplements and identify research needs. NIH responded by developing an evidence-based review program using the Evidence-Based Practice Centers Program established by the Agency for Healthcare Research and Quality to conduct systematic reviews of the scientific literature and prepare reports of their findings. These reports have resulted in the publication of a number of articles in the peer-reviewed literature, and have helped NIH make decisions on research priorities in these areas. NIH ICs have found these reports invaluable in presenting what is and is not known in a research area, thus laying a sound foundation for identifying gaps in knowledge and providing a strong scientific basis for the development of a research agenda and for informing health policy decisions. Currently, NIH is sponsoring an evidence report on *Vitamin D and Calcium: Systematic Review of Health Outcomes* that will be considered by the IOM committee established to assess current relevant data and update as appropriate the Dietary Reference Intakes for vitamin D and calcium.

- For more information, see <http://ods.od.nih.gov/Research/EvidenceReports.aspx>
- (E) (ODP/ODS)

ClinicalTrials.gov: ClinicalTrials.gov was significantly modified during FY 2008-2009 to respond to new clinical trial registration and results reporting requirements established by the FDA Amendments Act of 2007 (PL 110-85). The existing registry was expanded to accommodate the submission of more information about a larger number of trials, including those trials of FDA-regulated drugs, biological products and devices that now are required to register. In addition, NIH developed and implemented results modules to accept and display to the public summary results information, including adverse event information from registered trials. Mandatory reporting of results began in September 2008, with mandatory submission of adverse event information following in September 2009. During FYs 2008-2009, more than 34,000 trials were newly registered with ClinicalTrials.gov, raising the total number of registered trials to 80,000. In addition, summary results of more than 830 clinical trials were submitted and made available at ClinicalTrials.gov, with the rate of results submission approaching 200 trials per month by the end of FY 2009. To solicit input on issues to be considered in rulemaking for further expansion of ClinicalTrials.gov, a public meeting was held in

April 2009; more than 200 participants attended the meeting, and more than 70 written comments were submitted to a public docket.

- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (NLM)

Multicenter AIDS Study (MACS) Small Grant Opportunity: MACS is an ongoing (since 1984) epidemiological study in several U.S. cities of multi-ethnic/racial HIV-infected and HIV-uninfected men who have sex with men (MSM). A small grant funding opportunity is enhancing the value and potential for new knowledge from the MACS by examining drug use and HIV/AIDS among MSM over the life course. Studies will include an examination of social and behavioral risk factors and trajectories, the role of drug use in neurocognitive function, and other medical consequences. Findings from these studies may lead to new insights and interventions targeting this high-risk group. Such findings reinforce the importance of implementing interventions targeting drug reduction as part of comprehensive and efficacious HIV prevention program.

- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIAID, NIDA, NIMH)

A Variety of Approaches Help Children Overcome Auditory Processing and Language Problems: Almost 7 percent of school-age children have difficulties learning and using language. Childhood language impairments can have lifelong effects on an individual's social life, academic career, and job aspirations. Each year, more than 1 million public school children receive interventions to address their language impairments. One very popular intervention is a commercially available software program called Fast ForWord Language (FFW-L; Scientific Learning Corporation, 1998). NIH-supported scientists conducted a randomized controlled trial of more than 200 children with language impairments, to assess whether those who used FFW-L had greater improvement in language skills than those who used one of two other methods, plus an active control group. The children in all three intervention groups demonstrated statistically significant improvement in both auditory processing and language skills. Thus, FFW-L did not provide a significant advantage over other types of interventions delivered in a similar intensive manner. Surprisingly, children in the active control group, which received individualized attention, instruction, and computerized testing on academic subjects but did not receive language intervention, also demonstrated significant improvement in auditory processing and language skills. This study demonstrated that all four methods improved the children's auditory processing and language skills. The data suggest that intensive programs focusing individualized attention on children with language impairments can improve language skills and preempt lifelong communication difficulties.

- Tager-Flusberg H, Cooper J. *J Speech Lang Hear Res* 1999;42:1275-8. PMID: 10515521.
- Gillam RB, et al. *J Speech Lang Hear Res* 2008;51(1):97-119. PMID: 18230858. PMCID: PMC2361096.
- For more information, see http://www.nidcd.nih.gov/news/releases/08/01_30_08.htm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDCD, NICHD)

Liver Disease Research: NIH supports clinical research to address the spectrum of liver diseases. The Nonalcoholic Steatohepatitis Clinical Research Network conducts placebo-controlled clinical trials of treatments for this condition, both in adults given pioglitazone or vitamin E, and in children given metformin or vitamin E. The Hepatitis B Clinical Research Network will conduct clinical trials to evaluate the effectiveness of different treatments and learn more about the natural history of this disease. The Childhood Liver Disease Research and Education Network combines and expands previous consortia focused on biliary atresia and cholestatic liver disease. This new network will foster discovery of new diagnostic

Clinical and Translational Research

and treatment options for children with these diseases or who undergo liver transplantation, and support research training in rare pediatric liver diseases. Plans for another clinical network are beginning with a study to test whether immunosuppression minimization would be safe and thus beneficial in children several years after liver transplantation. The adult and pediatric Acute Liver Failure Study Groups address the problem of acute liver failure due to drugs or other factors. Current studies are testing potential therapies to improve survival. For example, results of a clinical trial to test intravenous N-acetylcysteine as a treatment for nonacetaminophen-related acute liver failure showed significant improvement in transplant-free survival in individuals who received therapy early in the course of their acute liver failure. The Drug-Induced Liver Injury Network conducts research aimed at understanding, diagnosing, and ultimately preventing liver toxicity due to drugs or complementary and alternative medicines. Future efforts of this network will focus on identifying genetic risk factors for drug-induced liver toxicity.

- Lee WM, et al. *Gastroenterology* 2009;137(3):856-64, 864.e1. PMID: 19524577.
- For more information, see <http://www.jhucct.com/nash/>
- For more information, see <http://diln.dcri.duke.edu/>
- For more information, see <http://www.utsouthwestern.edu/utsw/cda/dept25203/files/89624.html>
- For more information, see <http://www.palfstudy.org/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDDK, FDA, NCI, NICHD) (GPRA)

OHARA: The Oral HIV/AIDS Research Alliance: At the vanguard of basic, translational, and clinical research to combat the oral manifestations of HIV/AIDS is the NIH-funded Oral HIV/AIDS Research Alliance (OHARA), which drives and supports novel clinical studies in the United States and internationally to improve diagnosis, treatment, and management of comorbidities of AIDS-related oral complications, including necrotizing ulcers and tumors, fulminating fungal infections, and painful viral lesions that occur in almost all 33 million people infected worldwide. Their devastating effects compromise nutrition and exacerbate immune suppression in addition to the local effects. Even since the advent of antiretroviral therapy (ART), oral complications of AIDS remain a major public health problem. Though ART alleviates some symptoms, many oral lesions need additional specific treatment and globally, only 30 percent of HIV-infected individuals for whom ART is indicated receive it. The estimated prevalence of U.S cases of HIV/AIDS in 2006 exceeded 1.1 million, while about 56,300 people were newly infected with HIV that year. In its fourth year OHARA is making significant strides for people living with HIV/AIDS. OHARA is formed by world-expert scientists and clinicians. Its success is driven by three geographically and academically separate core units that provide expertise in epidemiology, mycology, and virology, embraced by a centralized NIH management and leadership. Currently, OHARA has ramped up eight clinical studies in various phases. They include studies to assess the clinical effectiveness of diagnostic tools for HIV/AIDS-related conditions, and compare the safety and efficacy of novel treatments and preventive strategies for HIV/AIDS-related oral diseases and malignancies.

- Shiboski CH, et al. *J Oral Pathol Med* 2009;38(6):481-8. PMID: 19594839.
- Jacobson MA, et al. *PLoS One* 2009;4(4):e5277. PMID: 19381272. PMCID: PMC2667217.
- For more information, see <http://aactg.org/committees/scientific/optimization-co-infection-and-co-morbidity-management/subcommittees/ohara-sub-3>
- For more information, see <http://www.nidcr.nih.gov/Research/DER/IntegrativeBiologyAndInfectiousDiseases/AIDSImmuno.htm>
- For more information, see <http://aactg.org/about-actg>
- For more information, see <http://www.who.int/hiv/data/en/>
- For more information, see <http://www.cdc.gov/hiv/topics/surveillance/basic.htm#Main>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIDCR, NIAID)

Research on Bariatric Surgery: The multicenter NIH-funded Longitudinal Assessment of Bariatric Surgery (LABS) consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Results from this study have been published in the *New England Journal of Medicine*. The study also addresses comparative effectiveness with respect to its collection of data on surgical procedures and pre- and post-operative information. Because bariatric surgery also is used in clinical practice sometimes as a treatment for severely obese adolescents, NIH additionally is supporting an observational study of teens already scheduled for surgery, Teen-LABS, to collect data to help determine whether it is an appropriate treatment option for extremely obese adolescents. A pilot study also is being conducted using the new Metabolic Clinical Research Unit at the NIH CC to examine changes in insulin resistance after bariatric surgery. To further explore the observation that certain bariatric surgical procedures are associated with amelioration of obesity-related insulin resistance and diabetes soon after surgery, and thus independent of weight loss, NIH issued a funding opportunity announcement to encourage research in this area.

- Adams TD, et al. *N Engl J Med* 2007;357(8):753-61. PMID: 17715409.
The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. *N Engl J Med* 2009;316(5):445-54. PMID: 19641201.
- For more information, see <http://win.niddk.nih.gov/publications/labs.htm>
- For more information, see <http://www.nih.gov/news/pr/apr2007/niddk-16.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E/I) (NIDDK, ORWH)

Urology Research: The Urinary Incontinence Treatment Network (UITN) conducts long-term studies and clinical trials of the most commonly used surgical, pharmacological, and behavioral approaches for management of urinary incontinence in women diagnosed with stress and mixed incontinence. Recently, a different group of investigators completed the Program to Reduce Incontinence by Diet and Exercise (PRIDE) study and determined that a weight loss program could reduce significantly the frequency of urinary incontinence in overweight and obese women. Several studies address interstitial cystitis/painful bladder syndrome (IC/PBS), a urologic condition whose prevalence is uncertain and which remains difficult to diagnose and treat. The RAND Interstitial Cystitis Epidemiology (RICE) study is designed to estimate the prevalence of interstitial cystitis and establish a working definition of this condition. The Boston Area Community Health (BACH) Survey is a population-based study of urologic conditions, including IC/PBS, in more than 5,500 adults. Results emerging from BACH about IC/PBS will provide a clearer picture on the IC/PBS burden in the population, and will inform research efforts to reverse this burden. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is designed to enhance understanding of the major urological chronic pelvic pain disorders, including IC/PBS and chronic prostatitis/chronic pelvic pain syndrome.

- Burgio KL, et al. *Ann Int Med* 2008;149:161-9. PMID: 18678843.
Subak LL, et al. *N Eng J Med* 2009;360(5):481-90. PMID: 19179316.
- For more information, see <http://www.uitn.net/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIDDK, NICHD)

Improving the Lives of Asthmatic Children in the Inner City: The NIH Inner-City Asthma Consortium (ICAC) of 10 academic clinical centers, launched in 2002, evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. The Consortium also pursues studies to understand mechanisms underlying the onset and progression of asthma and research to develop diagnostic and prognostic biomarkers. An ICAC longitudinal birth cohort study involving 500 inner-city children is investigating the immunologic causes of the development of recurrent wheezing, which can be indicative of asthma in children under age 3. ICAC has

Clinical and Translational Research

extended the study to follow all participant children to age 7, when the diagnosis of asthma can be definitive. Researchers hope to identify immunologic characteristics that will predict the development and severity of asthma at a later age. ICAC researchers are conducting two clinical trials to determine the safety, dosing levels, and biologic activity of a potential new allergy immunotherapy for cockroach allergen, which ICAC studies previously found to be a major determinant of asthma severity among inner-city children. Finally, an ICAC clinical trial assessed the benefit of using exhaled nitric oxide (NO) as a marker for asthma management. Although the study reinforced the importance of the NIH asthma guidelines for disease control, it did not find that measuring exhaled NO provided any additional clinical benefit.

- Szeffler SJ, et al. *Lancet* 2008;372(9643):1065-72. PMID: 18805335. PMCID: PMC2610850.
- For more information, see <http://www3.niaid.nih.gov/topics/asthma/research/researchActivities.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
- (E) (NIAID)

Rural Latino Preschooler's Oral Health: Intersections among Family, Community, Providers and

Regulators: Latino children experience among the highest prevalence of early childhood dental caries in the United States. Researchers explored the intersections among four societal sectors or contexts of care that potentially contribute to oral health disparities for low-income, preschool Latino children in rural California. The ethnographic investigation was conducted in a predominately Mexican-American agricultural community. Observations occurred in homes, community facilities, and dental offices, and were supplemented with in-depth interviews by trained anthropologists with key community informants and primary caregivers of children less than 6 years old. Factors that significantly intersected to produce or sustain poor oral health care for children follow. Caregivers did not always recognize signs of decay among their children, nor quickly respond unless children also complained of pain. Fluctuating eligibility for health insurance intersected with limited community infrastructure and civic amenities, including lack of public transportation, to create difficulties in access to care. Nonfluoridated bottled water often was consumed rather than tap water because of fears about potential pesticide pollution of the municipal water supply. Multiple dental visits caused parental hardship and occasionally resulted in the loss of the caregiver's job. Dental fear and poor provider-caregiver communication were exacerbated by a scarcity of dentists willing to serve rural low-income populations. Such empirical research related to newly emerging conceptual models is greatly needed. Understanding that multiple, intersecting factors at numerous levels will inform intervention research customized to the individual, community, and society.

- Barker JC, Horton SB. *BMC Oral Health* 2008;8:8. PMID: 18377660. PMCID: PMC2362117.
- For more information, see <http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/DentalCaries/DentalCariesChildren2to11>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NIDCR)

Alzheimer's Disease Cooperative Study (ADCS): Much of the AD-related clinical research supported by NIH takes place through the ADCS. The study involves a consortium of centers in the U.S. and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of AD or predict development of the disease in vulnerable people. To date, approximately 4,600 people have participated in the trials. Five new trials are underway through ADCS. These include: (1) a trial to examine whether treatment with DHA, an omega-3 fatty acid, will slow decline in AD; (2) a multicenter trial to evaluate home-based assessment methods for AD prevention research in people age 75 or older; (3) a trial to evaluate the efficacy and safety of 18 months of treatment with the drug PF-04494700 (TTP488), an oral compound formulated to prevent amyloid beta from binding to a specific brain receptor; (4) a trial of valproate, an anticonvulsant drug, to determine its ability to delay the emergence of agitation and psychosis and possibly the clinical progression of AD; and (5) a trial of intravenous immunoglobulin, which contains naturally occurring antibodies against beta-amyloid, to establish its clinical utility for treating AD. This program is a cornerstone of the NIH

GPRA goal to: "By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

- For more information, see <http://www.adcs.org/Default.aspx>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIA) (GPRA)

Interventions to Remediate Age-Related Cognitive Decline: Age-related cognitive decline distinct from dementia will affect most older individuals to some extent and has a direct impact on their independence and vitality. Cognitive training, physical exercise, enhancement of self-efficacy, social engagement, diet, environmental enrichment, and stress reduction have all been shown to have positive effects on cognition; however, the quality of this evidence varies widely across studies. NIH, in partnership with the McKnight Brain Research Foundation in conjunction with the Foundation for NIH, has initiated a program to convert insights from previous work in cognitive aging into feasible intervention strategies that can be tested in randomized clinical trials. The program's primary goal is to support the initial development and pilot testing of behavioral interventions (individually and in combination) to establish their feasibility, the likely strength of their effects, and immediate and short-term efficacy. These early steps should allow these interventions to move to new clinical trials.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-09-009.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIA)

Comparative Effectiveness Study of Drugs for Age-Related Macular Degeneration: Lucentis was approved by FDA in 2006 for treatment of advanced age-related macular degeneration (AMD), a leading cause of vision loss in older Americans. Though the drug is safe and effective, it is expensive—approximately \$2,000 per month—and repeated injections are required. Avastin is a similar pharmaceutical but is far less expensive—approximately \$100 per month—and also has been used extensively in treating patients with AMD. Most retinal specialists think that Avastin is a safe and effective alternative to Lucentis. To resolve this question, NIH is funding the Comparison of AMD Treatments Trial (CATT), a multicenter, randomized, clinical trial to compare the safety and efficacy of Avastin and Lucentis, and to explore less-frequent treatment schedules for both drugs. The first participants were randomized in early 2008. If Avastin proves to be comparable to Lucentis, the cost savings could reach \$2-3 billion per year. Less frequent treatment schedules also would lower costs, reduce treatment risk, and improve patient quality-of-life.

- For more information, see <http://www.nei.nih.gov/news/pressreleases/022208.asp>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NEI)

Promising Clinical Trials of Gene Transfer for Severe Childhood Eye Disease: Leber congenital amaurosis (LCA) is an early-onset, severe retinal disease that results from mutations in any 1 of 13 genes. One form of LCA results from mutations in a gene called RPE65. In 1993, NIH intramural scientists discovered that RPE65 plays a key role in the visual cycle, the set of biochemical interactions that converts light into an electrical signal to initiate vision. Mutations in RPE65 were found to disrupt the visual cycle, resulting in LCA and blindness. Retinal cells in children with LCA remain viable for several years, providing a window of opportunity to intervene therapeutically. An NIH-supported Phase I clinical trial of RPE65 gene transfer in LCA found the treatment is safe and that visual function improved. Two other independent Phase I clinical trials of RPE65 gene transfer also found evidence of visual improvement, but further work is needed to

Clinical and Translational Research

develop the therapeutic potential fully. Ongoing studies are exploring the range of therapeutic doses in adult and adolescent patients as well as rigorous evaluation of the effectiveness of this treatment. Gene transfer is particularly well-suited to the treatment of eye disease. This clinical trial is an important step in treating LCA and in establishing proof-of-concept for gene transfer as a viable therapy for eye disease.

- Cideciyan AV, et al. *Proc Natl Acad Sci U S A* 2008;30;105(39):15112-7. PMID: 18809924. PMID: PMC2567501.
- For more information, see <http://www.pnas.org/content/105/39/15112.long>
- For more information, see <http://www.nei.nih.gov/lca/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NEI)

Clinical Research Networks: Clinical research is essential for translating laboratory findings into evidence-based interventions targeting an array of public health concerns. Many research programs involve collaborative networks, drawing scientists together to bring the benefits of clinical research to high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. Among such networks that have generated significant findings to advance medical practice and improve public health are the Maternal and Fetal Medicine Network, Neonatal Research Network, Obstetric Pharmacology Research Network, Pediatric Critical Care Research Network, Pelvic Floor Disorders Network, Traumatic Brain Injury Clinical Trials Network, and Global Network for Women's and Children's Health Research.

- For more information, see <http://www.bsc.gwu.edu/mfmu/index.html>
- For more information, see <https://neonatal.rti.org>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-002.html>
- For more information, see <http://www.cpcrm.org>
- For more information, see <http://www.pfdnetwork.org>
- For more information, see <http://www.tbi-ct.org/>
- For more information, see <http://gn.rti.org/about/index.cfm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NICHD, FIC, NCCAM, NCI, NIDCR, ORWH)

Clinical Trials Network: NCI-supported clinical trials networks share resources and pool data to promote and support the study of new cancer treatments, methods of cancer prevention and early detection, and quality-of-life and rehabilitation issues. The 65 NCI-designated Cancer Centers serve as a major platform for these trials. NCI is restructuring the Clinical Trials Enterprise. Initiatives include: Standard Terms of Agreement for Research Trials, the Clinical Trials Reporting Program, correlative studies (e.g., biomarkers, imaging, and quality-of-life studies) embedded in clinical trials, disease-specific and patient advocate steering committees, and acceleration of translational research. The Community Clinical Oncology Program recently stopped the Selenium and Vitamin E Cancer Prevention Trial. Initial data analysis showed that selenium and vitamin E supplements, taken either alone or together for an average of 5 years, did not prevent prostate cancer. Recent findings from NCI's Cooperative Group Program include a gene abnormality that predicts childhood leukemia relapse, the role of the ch14.18 monoclonal antibody in the treatment of high-risk neuroblastoma, and the usefulness of CT colonography in detection of large adenomas and cancers. Year 2 accomplishments of the NCI Community Cancer Centers Program include increased patient and physician involvement in NCI-sponsored trials, new methods for tracking minority accrual, and improved specimen collection. The Pediatric Oncology Branch of the NCI Center for Cancer Research (CCR) is coordinating a neurofibromatosis clinical trials program to develop effective therapies for this disease. The CCR also is conducting trials for patients with androgen-independent and metastatic prostate cancer using anti-angiogenic compounds as well as novel immunotherapies and immunologic strategies.

- For more information, see <http://restructuringtrials.cancer.gov/>
- For more information, see <http://prevention.cancer.gov/programs-resources/groups/copt/programs/about>
- For more information, see <http://www.cancer.gov/clinicaltrials/digestpage/SELECT/>
- For more information, see <http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group>
- For more information, see http://target.cancer.gov/newsroom/news/01_07_09.aspx
- For more information, see <http://ncccp.cancer.gov>
- For more information, see <http://content.nejm.org/cgi/content/full/359/12/1207>
- For more information, see <http://ccr.cancer.gov>
- This example also appears in Chapter 2: *Cancer*
- (E) (NCI) (GPRA)

NIH Undiagnosed Diseases Program (UDP): In May 2008, NIH launched a program to evaluate patients with disorders that have evaded a diagnosis. Often patients seek help from multiple physicians and other health care providers over many years without receiving a diagnosis. Using a unique combination of 35 NIH scientific and medical specialty experts, the UDP pursues three goals: To help patients with unknown disorders reach an accurate diagnosis, to discover new diseases that provide insight into human biology, and to reestablish the NIH CC as the referral Center for mystery diseases. In its first year, the UDP received more than 2,000 inquiries, with approximately half of them of neurological origin, and 100 of them pediatric. Of the 2,000 inquiries in the first year, 850 were followed up with submission of medical records; 450 of the applications to participate in the program were deemed inappropriate; and 158 cases were accepted into the program by 10 Institutes and Centers. The program is trans-NIH in scope. Senior attending physicians with many different medical specialties from NIH research Centers and Institutes contribute the expertise needed to achieve the goals of this clinical research program. Any longstanding medical condition that eludes diagnosis by a referring physician can be considered undiagnosed and may be of clinical interest.

- For more information, see <http://rarediseases.info.nih.gov/Resources.aspx?PageID=31>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (ODP/ORDR, CC, NHGRI, NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIMH, NINDS, NINR)

Specialized Centers of Research (SCORs) on Sex and Gender Factors: The SCORs on Sex and Gender Factors Affecting Women's Health provide an innovative and interdisciplinary approach to advancing research on the influence of sex and gender as it relates to health and disease. Each of these SCORs emphasizes research in an area of clinical importance to women's health. The 11 current SCORs, co-funded with five NIH ICs and the Food and Drug Administration, address sex/gender research in the areas of depression, pain, urinary tract infection, reproductive issues, substance abuse, and osteoporosis. An example of scientific advances includes the isolation of an estrogen receptor alpha signaling process that therapeutically could be downregulated to reduce the risk for obesity and type 2 diabetes in menopausal women. In 2009, the SCORs contributed 116 journal articles, 176 abstracts, and 63 other publications (reviews and book chapters) resulting from their research.

- For more information, see <http://orwh.od.nih.gov/interdisciplinary/SCORs.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (ORWH, FDA, NIAMS, NICHD, NIDA, NIDDK, NIMH)

Compliance with the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research: NIH works to ensure compliance with the NIH Policy for the Inclusion of Women and Minorities as Subjects in Clinical Research by convening a trans-NIH committee that addresses consistency in inclusion policy implementation and investigator reporting of population data. Over the past 2 years, NIH has focused on analyzing and streamlining the data reporting process, reemphasizing the vital role of NIH staff to monitor adherence of the NIH Inclusion policy and management of grants, contracts, and cooperative agreements that involve human subjects research. The role of peer

Clinical and Translational Research

reviewers and investigators in meeting policy requirements continues to be stressed. NIH compiled the annual aggregate comprehensive reports: *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research* and the *2009 Biennial Report Certifying IC Compliance with the Inclusion Guidelines* based upon IC Advisory Council reviews, as required by statute.

- For more information, see <http://orwh.od.nih.gov/inclusion.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E/I) (**ORWH**, OER, OIR)

Developing Biodefense Vaccines and Therapeutics: NIH is the lead Federal agency within HHS for conducting and supporting research on potential agents of bioterrorism and emerging infectious diseases that directly affect human health. NIAID is the lead Institute within NIH in this area. Counter measures against NIAID Category A-C priority pathogens, microbes, and toxins, which are considered to be the most significant threats to the Nation's well-being, are either nonexistent, of limited utility, or threatened by the emergence of antimicrobial resistance or intentional engineering to increase virulence or decrease drug susceptibility. Given the absence of a substantial commercial market, regulatory hurdles, and extensive clinical trial requirements, the private sector has little incentive to invest in countermeasures. To remedy this situation, NIH supports unique partnerships among government, industry, small businesses, and academia to facilitate the movement of promising products through all stages of the drug research and development pipeline, with the goal of developing vaccines and therapeutics against diseases such as smallpox and botulism, as well as for infections with Ebola, Marburg, and West Nile virus infection. NIH advances include progress toward vaccines and/or therapeutics for anthrax, smallpox, and West Nile viruses. NIH supported development of a nonhuman primate model for plague; studies in the model have been completed for three licensed antibiotics for plague. In addition, advanced development and production continues for a recombinant protective antigen vaccine for anthrax and a modified vaccinia Ankara vaccine for smallpox.

- For more information, see <http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E/I) (**NIAID**)

NIEHS Clinical Research Unit: NIEHS focuses its research mission on environmental effects on human health, an area where human research data often are lacking. To improve the translation of basic research to human health, the NIEHS is expanding its Clinical Research Program (CRP). NIEHS has opened a new Clinical Research Unit (CRU) on the Research Triangle Park, NC, campus. The mission of the CRP is to translate basic laboratory findings to humans; study interactions between genetic susceptibility and environmental factors in the pathogenesis of complex human traits and diseases; and identify populations at risk and develop novel preventative and therapeutic strategies to combat human diseases. The CRU will provide support for the development of clinical research protocols; provide patient screening, recruitment and enrollment functions for NIEHS clinical studies; provide basic sample processing support (e.g., clinical labs and cell isolation); and provide support for specialized clinical procedures and services with the ultimate vision of fostering substantial onsite clinical research activity. Examples of the kinds of studies that will be supported by the CRU include the following: collection of tissue and body fluid samples for *ex vivo* human studies; investigation of host response to environmental exposures; Phase I-II-III clinical trials; environmental intervention studies; and phenotyping of selected individuals from NIEHS research populations such as the Environmental Polymorphism Registry. The CRU will be an integral part of the NIEHS intramural research portfolio and will provide support to a substantial number of NIEHS scientists.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (I) (**NIEHS**)

Putting Clinical Research Results into Practice

Genotyping Information for Use in Warfarin Therapy: The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), a component of the Pharmacogenetics Research Network (PGRN), sponsors data-sharing consortia. In 2009, one of the consortia, the International Warfarin Pharmacogenetics Consortium (IWPC), completed its first project: Clinical and genetic data from more than 4,000 patients worldwide who received warfarin were assembled into a large dataset to create a universal dose algorithm that incorporated genetic factors along with clinical factors. This established a better method to calculate the initial dose of the anticoagulant, and NIH will use the information for a prospective clinical trial to determine the value of pre-prescription genotyping. Further genomic analyses of the warfarin data set are underway. Based upon the success in this endeavor, more consortia were created in 2009. The International Tamoxifen Pharmacogenetics Consortium (ITPC) was formed to gather genetic and clinical data on the efficacy and toxicity of tamoxifen from patients around the world to test for specific associations between genetic variants and clinical effects, and the International Severe Irinotecan Neutropenia Consortium (INSINC) was formed to assemble a large dataset to answer questions definitively relating to genetic effects on adverse outcomes of irinotecan therapy, and to provide tools for evaluating toxicity risk.

- International Warfarin Pharmacogenetics Consortium, et al. *N Engl J Med* 2009;360(8):753-64. PMID: 19228618. PMCID: PMC2722908.
- For more information, see <http://www.nigms.nih.gov/Initiatives/PGRN>
- For more information, see <http://www.pharmgkb.org/views/loadConsortia.action>
- This example also appears in Chapter 3: *Genomics*
- (E) (NIGMS, NCRR, NHLBI, NINDS) (GPRA)

Workshop on Assessing Cost-Effectiveness in Clinical Research: Cost-effectiveness analysis (CEA) has been an ongoing element of the NIH clinical research portfolio for many decades. It is a close relative of comparative effectiveness research and, as a tool, can be applied usefully to data from either efficacy or effectiveness studies. CEA accounts for a small but important proportion of overall NIH research expenditures, totaling \$49 million in FY 2008. It comprises a relevant issue for scientists, health care providers, patients, families, and caregivers. In continuing its research tradition, in July of 2008, NIH hosted a workshop titled, "Integrating Cost-Effective Analysis into Clinical Research" in order to build a foundation for identifying interventions that will improve both health outcomes and the cost effectiveness of treatments. Building on workshop results, NIH issued the RFA "Incorporating Cost-Effectiveness Analysis into Factors Affecting Quality-of-Life Health Related Research (R01)" (RFA-NR-09-005). This Funding Opportunity Announcement solicits applications to study the cost effectiveness of interventions that will improve health outcomes.

- For more information, see <http://www.ninr.nih.gov/NewsAndInformation/MeetingSummariesandReports>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-09-005.html>
- (E, O) (NINR, NCI, ODP/ODS, ODP/ORDR)

NIH Consensus Development Program: This program, administered by the Office of Medical Applications of Research (OMAR) within the Office of the Director, NIH, was established in 1977 as a mechanism to assess, translate, and disseminate the results of biomedical research. Since its inception, OMAR has conducted more than 120 Consensus Development Conferences, and 30 State-of-the-Science (formerly "Technology Assessment") Conferences. The program generates evidence-based statements addressing controversial issues in medicine and public health that are useful and relevant for health care providers, policymakers, patients, researchers, and the general public. The conferences are structured around key questions, including questions on the efficacy, risks, and clinical applications of a technology, along with current gaps in knowledge to help formulate directions for future research. For every conference, a systematic evidence review is performed through a partnership with the Agency for Healthcare Research and Quality to serve as the foundation upon which the conference will build. Experts in the field provide additional input and insights through several

Clinical and Translational Research

days of oral presentations. The conferences also contain sessions for public input and discussion. A multidisciplinary, nonadvocacy, independent panel free from scientific or financial conflicts considers all of this information, and then writes a statement answering the posed conference questions. Consensus and state-of-the-science statements are disseminated widely after the conference to either impact clinical practice—when evidence strongly supports the use (or avoidance) of a particular intervention—or to direct future research—when important gaps in knowledge have been identified. Upcoming conferences in 2010 include: Enhancing Use and Quality of Colorectal Cancer Screening; Lactose Intolerance and Health; Vaginal Birth After Cesarean: New Insights; Preventing Alzheimer's Disease and Cognitive Decline; and Inhaled Nitric Oxide Therapy for Preterm Infants.

- For more information, see <http://consensus.nih.gov/>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (ODP/OMAR)

Family Satisfaction During Decisions to Withdraw Life Support: Clinicians in the intensive care unit (ICU) often care for patients who are on several life support measures simultaneously. When such a patient is dying and the decision is reached to withdraw life support, these clinicians may make an imperfect compromise in seeking to balance the complex needs of the patient and the patient's family—they may remove the life support measures one at a time over a period of days, rather than withdrawing all at once. This practice, referred to as sequential withdrawal, may be relatively common, and may have a varying impact on the family's satisfaction with ICU care. The research team examined the life support withdrawal process for 584 patients who died in the ICU or within 24 hours of discharge from the ICU, and surveyed the family members regarding their perceptions of the care provided. When surveyed 1 to 2 months after the death of the patient, family members of patients who had a short ICU stay reported a lower satisfaction with the ICU care if the withdrawal process was extended over more than 1 day. However, for family members of patients who had a long ICU stay (8 days or more), satisfaction with care increased with a more extended duration of the withdrawal. In addition, family satisfaction with care was higher if the patient was off the ventilator at the time of death. Withdrawal of life support is a complex process that depends on patient and family characteristics; however, sequential withdrawal of life support is a frequent phenomenon that sometimes seems to be associated with family satisfaction.

- Gerstel E, et al. *Am J Respir Crit Care Med* 2008;178(8):798-804. PMID: 18703787. PMCID: PMC2566791.
- For more information, see <http://www.nih.gov/news/health/oct2008/ninr-15.htm>
- For more information, see <http://www.ncbi.nlm.nih.gov/pubmed/18703787>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NINR)

Centers in Self-Management or End-of-Life Research: Future progress in improving the ability of those with chronic disease at all stages of life to manage their own illness, as well as improving the care of patients at the end of life, will require the development of enhanced research capacity, including more trained investigators and expanded institutional resources. In early 2007, NIH solicited applications for the Centers in Self-Management or End-of-Life Research. These Centers are expected to serve as a nexus for the emergence of self-management and end-of-life research as interdisciplinary sciences. They will train investigators from multiple backgrounds and leverage collaborations to increase the quantity and quality of innovative, interventional research projects. To date, six grants have been awarded from this solicitation. These Centers focus on a variety of topics, such as the self-management of chronic illnesses in Hawaii, biobehavioral research in self-management of cardiopulmonary disease, evidence-based practice in the underserved, and end-of-life transition research.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-004.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-005.html>

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NINR)

Support for Research on the Dissemination, Implementation, and Operation of HIV Preventive Interventions: NIH continues to support research on all aspects of HIV preventive interventions. While effective preventive interventions have been developed, there is a recognized gap between their development and their later uptake by community-level service providers. In FY 2008, NIH issued a funding opportunity announcement (FOA) to encourage research ensuring that these interventions are adopted and effectively implemented. The FOA invites applications for research projects that will enhance technology transfer, dissemination, implementation, and operational research related to evidence-based HIV preventive interventions. Staff from NIH and the Centers for Disease Control and Prevention collaborated in the development of this FOA by identifying research gaps and opportunities in these areas. Five categories of projects, in particular, were identified in which additional research activities could assist in the effective and efficient implementation of HIV preventive interventions: dissemination strategies, adoption of interventions, implementation fidelity and adaptation, intervention effectiveness, and sustainability of interventions.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-166.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIMH, CDC, NICHD, NINR)

Rapid HIV Testing Clinical Trial: HIV testing is an important component of HIV prevention. To help prevent late diagnosis and HIV spread, NIH is working to identify and address the cultural barriers to making HIV screening more acceptable and to strengthen the link between education, testing and counseling, and treatment within all ethnic groups. NIH-supported modeling research has shown that routine HIV screening, even among populations with prevalence rates as low as 1 percent, is as cost-effective as screening for other conditions such as breast cancer and high blood pressure. Still, little is known about whether offering testing in the absence of counseling influences patient acceptance or how they receive results. How and whether testing absent counseling influences HIV risk behaviors among those who are HIV negative also remains to be determined. Indeed, the Institute of Medicine has recommended comparison research to include significant prevention counseling as a key variable. In this regard, a randomized controlled clinical trial—taking place in NIH's Drug Abuse Treatment Clinical Trials Network—is recruiting individuals receiving drug abuse treatment to participate in a multicenter HIV testing and counseling study. The study will assess the relative effectiveness of on-site HIV rapid testing with brief, participant-tailored prevention counseling as compared with (1) on-site testing with information only and (2) referral for off-site HIV testing. HIV screening has important public health implications, recognized by the Centers for Disease Control and Prevention, which has called for increased HIV screening as part of its recommended guidelines. NIH is eager to advance new HIV rapid-screen technologies and counseling in community drug treatment programs and in criminal justice settings.

- For more information, see <http://www.drugabuse.gov/about/organization/arp>
- For more information, see <http://www.drugabuse.gov/CTN/protocol/0032.html>
- For more information, see <http://www.drugabuse.gov/about/organization/arp>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIDA)

HIV Topical Microbicides: Topical microbicides are small molecule prophylactic treatments to prevent the transmission and spread of HIV. Guided by the NIAID Topical Microbicide Strategic Plan, NIH is funding a number of microbicide research studies through the Microbicide Trials Network (MTN), the HIV Prevention Trials Network (HPTN), and the Microbicide Innovation Program (MIP). The microbicides under investigation are designed to prevent HIV transmission by killing or inactivating microbial pathogens, strengthening the body's normal defenses, blocking attachment of HIV to

Clinical and Translational Research

susceptible cells, and preventing HIV from spreading to other uninfected cells. Microbicides typically are administered via a gel, foam, or cream intended to prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically inside the vagina or rectum. In February 2009, NIH-supported researchers found that an investigational vaginal gel called PRO 2000, intended to prevent HIV infection in women, is safe and approximately 30 percent effective (33 percent effectiveness would have been considered statistically significant). While additional data are needed to determine if PRO 2000 protects women from HIV infection, it was the first human clinical study to suggest that a microbicide may prevent male-to-female sexual transmission of HIV infection.

- For more information, see <http://www3.niaid.nih.gov/topics/HIVAIDS/Research/prevention/research/Microbicides/research.htm>
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/HPTN_035_gel.htm
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIAID, NICHD, NIMH)

Veterans With HIV and Alcohol Problems: The Veteran's Aging Cohort Study (VACS), a cooperative agreement between NIH and the Department of Veterans Affairs, focuses on HIV-infected veterans with alcohol use disorders. Alcohol abuse and dependence occur in approximately 25 percent of veterans. This work informs the design of interventions to modify the risk of alcohol- and liver-related mortality associated with HIV. The VACS index, which predicts health outcomes including HIV disease progression, was developed and is being evaluated as a clinically informative index for this study. Alcohol measures that can be used readily in HIV clinical settings have been validated and will guide the intensity of the alcohol intervention. Determining the presence of other health comorbidities and the level of antiretroviral adherence will help prioritize clinical care. Collaborations between VACS and other large studies will determine the generalizability of studies with veterans to other populations and inform use of electronic medical records from clinical samples with complex diseases for scientific research. This study also has evaluated the associations of "non-HIV" conditions (e.g. HCV, cardiovascular health) with alcohol, HIV, HIV treatment, and aging, and contributed data to all three international cross cohort collaborations—North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), ART Cohort Collaboration (ART-CC), and HIV Cohorts Analyzed Using Structural Approaches to Longitudinal data (HIV CAUSAL)—addressing the question of when to start antiretroviral therapy. Progress of the VACS Study includes: enrollment of 7,015 patients, launch of a fourth follow-up survey (February 2008), and completion of blood and DNA collection and the initiated dissemination of tissue samples to researchers across the country. VACS also participates in collaborative grants, including those from the Veterans Affairs Health Services Research and Development Service, NIH, and the Medical Research Council UK.

- For more information, see <http://www.vacohort.org>
- For more information, see <http://statepiaps.jhsph.edu/naaccord/>
- For more information, see <http://www.epi.bris.ac.uk/art-cohort/index.htm>
- For more information, see <http://www.hsph.harvard.edu/faculty/miguel-hernan/hiv-causal>
- (E) (NIAAA)

BARI 2D Clinical Trial: Cardiovascular disease (CVD) is the leading cause of diabetes-related deaths—about 65 percent of people with diabetes die of heart disease or stroke. Recognizing the importance of comparative effectiveness research, NIH in FY 2000 awarded support for the BARI 2D clinical trial to evaluate management strategies for patients with stable coronary artery disease and type 2 diabetes. Its goal was to determine whether mortality and CVD event rates could be reduced by early coronary revascularization and intensive medical therapy compared with intensive medical therapy alone, and by an initial strategy of insulin sensitization compared with provision of insulin to treat hyperglycemia. The trial found that neither early revascularization nor insulin sensitization was superior to the tested alternatives in terms of CVD event rates. However, among patients for whom bypass surgery was deemed to be the appropriate revascularization procedure, prompt revascularization reduced the rate of major, nonfatal CVD events such as heart attack and stroke.

- BARI 2D Study Group, et al. *N Engl J Med* 2009;360(24):2503-15. PMID: 19502645.
- For more information, see <http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?>
- For more information, see <http://content.nejm.org/cgi/reprint/360/24/2503.pdf>
- For more information, see <http://content.nejm.org/cgi/reprint/360/24/2570.pdf>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NHLBI, NIDDK)

Action to Control Cardiovascular Risk in Diabetes (ACCORD): ACCORD is a multicenter randomized clinical trial of 10,251 persons with type 2 diabetes who are at high risk of a cardiovascular disease (CVD) event. It was designed to assess whether the rate of major CVD events could be reduced by intensive control of blood sugar (glycemia) compared with the current standard of care, intensive control of blood pressure compared with the current standard of care, or treatment of blood lipids with fibrates plus statins compared with treatment with statins alone. On February 6, 2008, NIH announced that participants receiving intensive glycemia treatment would be transitioned to the ACCORD standard treatment approach because higher mortality was observed among them. The glycemia main results were published in the *New England Journal of Medicine* in June 2008. They have substantial implications for the clinical treatment of diabetes, especially in older patients at high risk of CVD. The blood pressure and lipid trials are continuing as designed, with the last patient visits completed in June 2009.

- Action to Control Cardiovascular Risk in Diabetes Study Group, et al. *N Engl J Med* 2008;358(24):2545-59. PMID: 18539917.
- For more information, see <http://clinicaltrials.gov/ct2/show/>
- For more information, see <http://www.accordtrial.org>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NHLBI, CDC, NEI, NIA, NIDDK)

Diabetes Prevention Program Outcomes Study (DPPOS) and Translational Research: The landmark NIH Diabetes Prevention Program (DPP) clinical trial showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk. This finding was true across all participating ethnic groups and for both men and women. The DPPOS is a long-term follow-up study of the DPP participants that is determining the durability of the interventions in preventing or delaying type 2 diabetes, and how the interventions affect the development of cardiovascular disease and other complications of diabetes. The DPP group was highly diverse (45 percent from minority ethnic and racial groups), and DPPOS will compare outcomes for women and men, and by age and ethnicity. Renewed in FY 2009 for a second 5-year phase, the DPPOS will enable researchers to better determine the lasting benefits of the interventions to diabetes prevention and/or the delay of onset. In addition, NIH is pursuing translational research efforts to develop more cost-effective methods of achieving the lifestyle change that delayed or prevented diabetes in the DPP, and better methods to identify those with prediabetes. For example, one translational effort is using the YMCA to deliver a DPP lifestyle intervention; data from a recent pilot study suggest that using the YMCA may be a low-cost way to deliver a lifestyle intervention to large numbers of people in the United States. Many of these translational research studies focus on minority populations disproportionately burdened by type 2 diabetes and by obesity, a significant risk factor for type 2 diabetes.

- For more information, see <http://www.bsc.gwu.edu/dpp/protocol.htmlvdoc>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-09-176.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-06-532.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
- (E) (NIDDK, CDC, IHS, NEI, NHLBI, NIA, NICHD, NINR, OBSSR, ORWH)

Clinical and Translational Research

Framework for Adherence Research: A Workshop: NIH organized and led an internal Adherence Research Network. The Network developed a formal evaluation plan for NIH's adherence research portfolio. As a part of the evaluation, NIH convened a think-tank style workshop, titled Framework for Adherence Research and Translation: A Blueprint for the Next Ten Years. The workshop was held March 9, 2008, in conjunction with the Third International Conference on HIV Treatment Adherence. The workshop participants discussed opportunities for future research on adherence as well as challenges to the field, including key methodological barriers that require a renewed public health effort to improve adherence to preventive and treatment regimens.

- For more information, see http://obssr.od.nih.gov/scientific_areas/health_behaviour/adherence/index.aspx
- (O) (OBSSR, NIMH)

Science of Dissemination and Implementation: More present than ever within the research community is the belief that to optimize public health we must not only understand how to create the best interventions, but how to best ensure that they are delivered effectively within clinical and community practice. This is the focus of dissemination and implementation research, and building this knowledge base is imperative to get the best return on decades of investment in biomedical, behavioral, and social sciences research. The goal of the January 28-29, 2009, NIH-sponsored conference on the Science of Dissemination and Implementation was to provide a venue for the research community to exchange ideas, explore contemporary topics, and identify concepts, methods, and strategies to build research and organizational capacity for dissemination and implementation science. The conference was intended to complement the program announcement, Dissemination and Implementation Research in Health, which supports innovative approaches to identifying, understanding, and overcoming barriers to the adoption, adaptation, implementation, and maintenance of evidence-based practices by health providers, insurers, policy makers, and the public, and is a follow-up to an earlier conference, Building the Science of Dissemination and Implementation in the Service of Public Health.

- For more information, see http://obssr.od.nih.gov/funding_opportunities/foas/index.aspx
- For more information, see http://obssr.od.nih.gov/news_and_events/conferences_and_workshops/DI2009/index.html
- (E) (OBSSR, FIC, NCI, NHLBI, NIDA, NIDCD, NIDCR, NIMH, NINR, ODP/ODS)

Oversight of Genetic Technologies: In its April 2008 report, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) identified gaps in the oversight of genetic testing and critical steps that should be taken to address them. The five key gaps in existing policy were: (1) regulations governing clinical laboratory quality; (2) oversight of the clinical validity of genetic tests; (3) transparency of genetic testing; (4) the level of current knowledge about the clinical usefulness of genetic tests; and (5) the ability of health professionals, the public health community, patients, and consumers to use these new tests effectively. Most immediately, SACGHS recommended the creation of a national registry of laboratory-developed tests that also would contain information about the tests' complexity and clinical validity and utility.

- For more information, see http://oba.od.nih.gov/policy/policy_issues.html#CRP_004
- (O) (OSP/OBA, ATSDR)

Research Training for Clinicians in Practice-Based Research Networks Yields Results: When NIH awarded 6 7-year grants to establish 3 dental practice-based research networks (PBRNs), its aim was to assemble teams of practicing dentists to investigate with greater scientific rigor "everyday" issues in the delivery of oral health care. The impetus behind the networks was the frequent lack of research data to guide treatment decisions in the dentist's office. One of the key objectives to accomplishing the goal is providing the participating clinicians, many of whom have had no previous

research experience, with the training and education needed to conduct clinical research effectively. The PBRNs have developed multiple methods of delivering research training to practicing clinicians, including training in research methods, protection of human participants, good clinical practice, research protocol development, and interpretation of research results. Descriptions of the training programs have been reported in national journals, and a collaboratively written chapter recently was accepted for publication in a textbook on PBRNs. The real proof of the value of research training, of course, is whether research relevant to clinical practice is occurring—yes it is. Over the course of the grant period, the networks each will complete approximately 15 to 20 short studies. In early 2009 almost 90 study concepts had been approved, more than 20 were underway, and several had been completed and reported. The citations below are limited to those that deal with research training.

- DeRouen TA, et al. *J Am Dent Assoc* 2008;139(3):339-45. PMID: 18310739.
- Gilbert GH, et al. *J Am Dent Assoc* 2008;139(1):74-81. PMID: 18167389.
- For more information, see <http://www.nidcr.nih.gov/Research/DER/ClinicalResearch/DentalPracticeBasedResearchNetworks.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDCR)

Disseminating Evidence-Based Health Information on Diabetes and Digestive and Kidney Diseases: The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational materials on diabetes and kidney disease, respectively. For example, the NDEP encourages people to take "small steps" to prevent type 2 diabetes. The NDEP also promotes the importance of comprehensive diabetes control in its "Control Your Diabetes. For Life" educational campaign. The NKDEP encourages African American families to discuss kidney disease at family reunions, and also provides tools and resources for health care providers to help coordinate care and improve patient outcomes for kidney disease. Both programs tailor materials for minority groups at high risk. Information Clearinghouses also provide key health information for patients, health care professionals, and the general public. A recent campaign highlighted the importance of using accurate methods to test hemoglobin A1c in people with diabetes who have sickle cell trait or other inherited hemoglobin variants. Other recent campaigns raised awareness of celiac disease and interstitial cystitis. The Weight-Control Information Network provides up-to-date, science-based information on weight control, obesity, physical activity, and related nutritional issues.

- For more information, see <http://www2.niddk.nih.gov/HealthEducation/>
- For more information, see <http://ndep.nih.gov/>
- For more information, see <http://nkdep.nih.gov/>
- For more information, see <http://win.niddk.nih.gov/>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (NIDDK, CDC)

Getting Proven Treatments into the Criminal Justice System: Unfortunately, most inmates in need of substance abuse treatment do not receive it while in prison and, upon their release, continue a vicious cycle of drug use and crime. In response, NIH—along with multiple Federal agencies and health and social service professionals—is working systematically to move science-based treatment interventions into the criminal justice system, where they can have a major impact. In a Delaware Work Release study, those who participated in prison-based treatment followed by aftercare were 7 times more likely to be drug free after 3 years than those who received no treatment. Other research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) affirms the critical need for prisoners to receive effective substance abuse treatment while incarcerated and during their re-entry into the community. A recent randomized clinical trial found that prisoners who began methadone maintenance treatment in prison were significantly more likely after 12 months post-release to continue treatment and decrease drug use and criminal activity than a

Clinical and Translational Research

counseling-only group. A related issue for this population is heightened HIV risk—the U.S. prison system also being where many inmates first receive HIV testing and initiate treatment. However, only a nominal percentage continues this treatment following release. New research shows that simply providing formal assistance in filing the paperwork for antiretroviral treatment medications can promote greater continuity of HIV pharmacotherapy among released inmates. Gaining insight into ways to reduce drug use and criminal recidivism—including among adolescents for whom the same issues apply—as well as limit HIV spread in communities means huge economic and social cost savings.

- Baillargeon J, et al. *JAMA* 2009;301(8):848-57. PMID: 19244192.
- Chandler RK, et al. *JAMA* 2009;301(2):183-90. PMID: 19141766. PMCID: PMC2681083.
- Kinlock TW, et al. *J Subst Abuse Treat* 2009;37(3):277-85. PMID: 19339140. PMCID: PMC2803487.
- Martin SS, et al. *Prison J* 1999;79(3):294-320.
- For more information, see <http://www.cjdat.org/>
- For more information, see <http://www.drugabuse.gov/Blending/>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Minority Health and Health Disparities*
- (E) (NIDA) (GPRA)

Understanding and Promoting Health Literacy: Low health literacy is a widespread problem, affecting more than 90 million adults in the United States, where 43 percent of adults demonstrate only the most basic or below-basic levels of prose literacy. Low health literacy results in patients' inadequate engagement in decisions regarding their health care and can hinder their ability to realize the benefits of health care advances. Research has linked low or limited health literacy with such adverse outcomes as poorer self-management of chronic diseases, fewer healthy behaviors, higher rates of hospitalizations, and overall poorer health outcomes. An NIH program announcement supports research that increases our understanding of the health literacy problem and its relationship to health disparities as well as the development of interventions to overcome the adverse consequences of low health literacy. In December 2008, a grantee meeting was convened to provide a venue for NIH-funded scientists conducting health literacy research to discuss lessons learned about health literacy-related topics, including measurement and methodology, actionable research (e.g., plain language, dissemination), and special populations (e.g., cognition, culture, and socioeconomic status). NIH is planning a fall workshop to highlight the state-of-the-science and to inform directions for reissuing the funding opportunity announcement in 2010.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-07-020.html>
- For more information, see http://obssr.od.nih.gov/scientific_areas/social_culture_factors_in_health/health_literacy/index.aspx
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (OBSSR, AHRQ, NCI, NHLBI, NIA, NIBIB, NICHD, NIDCD, NIDCR, NIEHS, NIMH, NINR, NLM)

Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer Care: The purpose of the Cancer Research Network (CRN) is to enhance research on cancer epidemiology, prevention, early detection, and control in the context of health care delivery systems. CRN combines established research groups affiliated with 14 health care delivery organizations that provide comprehensive care to a racially and ethnically diverse population of nearly 11 million individuals. CRN has developed strong research capabilities in several areas: developing and applying innovative methods to collect and interpret data from both conventional and electronic medical records systems; assembling large samples of patients with documentation of patient characteristics and longitudinal data on receipt of health services and clinical and quality-of-life outcomes; collecting and integrating complex data from patients, providers, and organizations to examine issues in health care delivery from multiple perspectives; quantifying the effect of key factors in the delivery process that may determine quality and outcomes of care; and conducting studies on behavioral and systems-based interventions to improve the delivery of care in community-based health care delivery systems. The Breast Cancer Surveillance

Consortium (BCSC) is a research resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. The BCSC is a collaborative network of seven mammography registries with linkages to tumor and/or pathology registries. The Consortium's database contains information on 7,521,000 mammographic examinations, 2,017,869 women, and 86,700 cancer cases.

- For more information, see <http://crn.cancer.gov>
- For more information, see <http://breastscreening.cancer.gov/>
- This example also appears in Chapter 2: *Cancer*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (NCI)

Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging: NIH supports 13 Roybal Centers whose objective is to improve the health, quality of life, and productivity of middle-aged and older people by facilitating translation of basic behavioral and social science to practical outcomes by developing new technologies and stimulating new "use-inspired" basic research in the behavioral and social sciences. Roybal investigators have made several key discoveries. For example: One Center has developed tools and technologies for identifying older adults at risk for automobile crash involvement, and is working with industry partners to develop and disseminate products based on these tools. Another Center has developed two evidence-based interventions from its in-depth work on physical activity for older adults. One program, Fit and Strong!, is targeted to older adults with lower extremity osteoarthritis, and one is targeted to older adults with developmental/intellectual disabilities (primarily Down syndrome). A Roybal investigator has developed instruments for self-efficacy appropriate for use with older adults with developmental/intellectual disabilities; these have been adopted internationally. Finally, a Center has developed a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Other companies have used this model to develop related products, and the model has spurred several new grant-funded research projects, including the development of a new medication tracker for older adults.

- For more information, see <http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/roybals.htm>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E) (NIA)

Genomic Medicine: One of the promises of the Human Genome Project is the personalization of medicine. The time rapidly is approaching when health care providers will be able to use information about each person's unique genetic makeup to develop individualized strategies for detecting, treating, and, ultimately, preventing disease. A number of initiatives are underway to explore this area, including the Multiplex Initiative, the Surgeon General's Family History Initiative, and the ClinSeq project. The Multiplex Initiative, a collaboration between NIH researchers, the Group Health Cooperative in Seattle, and the Henry Ford Health System in Detroit, studied the interest levels of healthy young adults in receiving genetic testing for eight common conditions. The purpose was to understand better how patients respond to the results of genetic tests. The U.S Surgeon General's Family History online tool, created through a collaborative effort involving the Office of the Surgeon General, NIH, the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, and the Health Resources and Services Administration, allows people to record health conditions that have affected their relatives. The tool uses a three-generation pedigree to organize family health information in a format that people can easily share with their health care providers and other family members. Such information can lead to more proactive strategies for preventing disease and improving health. Finally, NIH researchers and their collaborators are enrolling volunteers in the ClinSeq project, which is piloting large-scale medical sequencing in a clinical setting, with a focus on cardiovascular disease.

Clinical and Translational Research

- Guttmacher AE, et al. *N Engl J Med* 2004;351(22):2333-6. PMID: 15564550.
- For more information, see <http://www.multiplex.nih.gov>
- For more information, see <http://www.genome.gov/25521052>
- For more information, see <http://www.hhs.gov/familyhistory>
- For more information, see <https://familyhistory.hhs.gov>
- For more information, see <http://www.genome.gov/20519355>
- This example also appears in Chapter 3: *Genomics*
- (E, I) (**NHGRI**)

NIH and Comparative Effectiveness Research (CER): CER is the conduct and synthesis of research comparing the benefits and harms of different interventions to prevent, diagnose, treat, and monitor health conditions in real-world settings. (For the full HHS definition of CER, see *Comparing the Effectiveness of Different Therapies or Strategies* in the section of Chapter 3 on Clinical and Translational Research.) NIH has a long history of supporting landmark CER studies and of supporting CER research that challenges existing standards of clinical practice. NIH was awarded \$400 million of the \$1.1 billion allocated under auspices of the American Recovery and Reinvestment Act of 2009 for CER. An NIH "CER Coordinating Committee" was initiated to ensure optimal use of the stimulus funds, to make funding recommendations to the NIH Director, and to develop a long-term CER research plan for the future. The agency is working collaboratively with sister agencies (AHRQ, FDA, VA, etc.), is represented on the "Federal Coordinating Council for CER" (together with representatives from 15 Federal agencies and offices), and has consulted with the IOM regarding the drafting of its report on initial national priorities for CER. NIH plans to obligate the \$400 million to advance CER via "Challenge Grants," "Grand Opportunity Grants," expansion of scope of research, etc. The agency will further ramp up capacity by investing in development of innovative trial design for conducting CER, in advancing statistical and modeling approaches capable of mining multidimensional databases, in undertaking planning studies to support large-scale trials to speed critical breakthroughs, and in forging the unique infrastructure capable of supporting the CER studies of tomorrow. These investments will generate CER findings of public health significance, high relevance to clinical medicine, and scientific excellence.

- For more information, see <http://www.iom.edu/>
- For more information, see <http://www.hhs.gov/recovery/programs/os/cerbios.html>
- (O) (**OSP/OSPA, DPCPSI, NCCAM, NCI, NCMHD, NCRR, NHLBI, NIA, NIBIB, NIDDK, NIMH, NINDS, ODP**)

Collaboration, Education, and Genetic Test Translation Program for Rare Diseases (CETT): This research and education project was developed to make available genetic tests to patients from CLIA-certified laboratories. The vast majority of the known rare diseases are genetic disorders, thus genetic testing can be an essential part of the diagnosis and treatment continuum for rare diseases. The CETT program is a pilot program to translate new genetic tests from research in gene discovery to clinical practice and to meet an unfulfilled need for many rare diseases for which research did not translate to the development of a clinical diagnostic test. The mission of ORDR includes promoting the diagnosis of rare diseases and facilitating education in rare diseases. The CETT program encourages clinical laboratory and research collaborations, and supports the electronic collection of genetic and clinical data in public databases to leverage the information into new research and new treatments. During this pilot, the CETT program has supported the development of 34 genetic tests representing 67 diseases and 89 genes. The CETT Program also has piloted the development of educational materials about new test development for families and clinicians through the collaboration with advocacy and clinician experts in rare diseases and now is piloting the collection of de-identified clinical and genetic mutation information to be accessible publicly for the clinical and research community through partnership with NIH's National Center for Biotechnology Information. Tests put into development include DNM2 Centronuclear Myopathy, ROR2 Robinow Syndrome, ASPM, CDK5RAP2, CENPOJ, and MCPH1 for Autosomal Recessive Primary Microcephaly (University of Chicago); and ATPIA3 Rapid-Onset Dystonia Parkinsonism (Neurogenetics DNA Diagnostic Lab in

Boston). Other tests put into development earlier include Urea Cycle Disorders (Baylor College of Medicine); Inclusion Body Myopathy Associated with Paget Disease and/or Frontotemporal Dementia (University of California at Irvine); and Duchenne Muscular Dystrophy and Becker Muscular Dystrophy (Emory University).

- For more information, see <http://rarediseases.info.nih.gov/cettprogram/default.aspx>
- (O) (**ODP/ORDR**, NLM)

Translating CAM Research Results into Clinical Practice: Results from a National Survey of Physicians and CAM Providers: In an initial investigation of the potential for information from complementary and alternative medicine (CAM) research to influence clinical practice, a 2007 national survey asked acupuncturists, naturopaths, internists, and rheumatologists about their awareness of CAM clinical trials, their ability to interpret research results, and their use of research evidence in decisionmaking. The survey focused on awareness of two major NIH-funded clinical trials that studied acupuncture or glucosamine/chondroitin for osteoarthritis of the knee. According to the survey, more than half (59 percent) of the 1,561 respondents were aware of at least 1 of the 2 clinical trials, but only 23 percent were aware of both trials. A majority of respondents said they were "moderately confident" in their ability to interpret research literature; few—20 percent of acupuncturists, 25 percent of naturopaths, 17 percent of internists, and 33 percent of rheumatologists—said they were "very confident." All groups regarded clinical experience as "very important" in their decisionmaking, although CAM providers were more likely to rate it "most important." CAM providers were much more likely than physicians to rank research results as "least important," whereas physicians were much more likely to rate patient preferences as least important. The results of the survey demonstrate that CAM research has the potential to make a difference in both conventional and alternative medicine clinical practice. Concerted efforts are recommended to better train all clinicians in interpretation and use of evidence from research studies, and to improve the dissemination of research results.

- Tilburt JC, et al. *Arch Intern Med* 2009;169(7):670-7. PMID: 19364996.
- For more information, see <http://nccam.nih.gov/research/results/spotlight/041309.htm>
- (E) (**NCCAM**)

A Behavioral Intervention to Improve Obstetrical Care: Background: Implementation of evidence-based obstetrical practices remains a significant challenge. Effective strategies to disseminate and implement such practices are needed. Adopting new evidence-based clinical practices and adapting them to different countries requires careful planning and adjustment of existing models to local conditions. Use of evidence-based guidelines improves quality of care, the behavior of health care practitioners, and the health outcomes of patients. Advance: This research focused on evaluating an intervention to facilitate the adoption of evidence-based practices in Latin American maternity hospitals. Using a cluster-randomized controlled trial design, this research evaluated the behavior and attitudes of birth attendants with respect to two evidence-based recommendations for obstetrical practice: the selective use of episiotomy and active management of the third stage of labor. The intervention was associated with an increase in use of prophylactic oxytocin and a decrease in the use of episiotomy. The intervention also was associated with reductions in the rate of postpartum hemorrhage. Birth attendants' readiness to change also increased in the hospitals receiving the intervention. The effects on the use of episiotomy and prophylactic oxytocin were sustained 12 months after the end of the intervention. Significance: This study, supported by NIH's International Clinical Operational and Health Services Research Training Award, addresses an implementation barrier and highlights that the use of evidence-based guidelines can improve the quality of care and the behavior of health care practitioners.

- Althabe F, et al. *N Engl J Med* 2008;358(18):1929-40. PMID: 18450604.
- For more information, see <http://content.nejm.org/cgi/content/abstract/358/18/1929>
- For more information, see http://www.fic.nih.gov/programs/training_grants/icohrta/
- (E) (**FIC**)

Clinical and Translational Research

The Spine Patient Outcomes Research Trial (SPORT) for Low Back Pain: Before SPORT, many people who had chronic low back pain were conflicted about whether to undergo surgery; some were not sure surgery was worth the risk, while others feared that delaying surgery might cause even more damage. In the past 4 years, SPORT demonstrated that, indeed, surgery is superior to nonoperative treatments for the 3 most common causes of severe low back pain: intervertebral disk herniation and lumbar spinal stenosis with or without degenerative spondylolisthesis (the slipping of vertebrae). However, people who have one of these conditions are not subjecting themselves to further harm if they adopt a "wait-and-see" approach before committing to surgery. The benefits of surgery to correct spinal stenosis, for example, were apparent as early as 6 weeks after surgery. Those patients who had severe slippage and discomfort due to lumbar spinal stenosis with degenerative spondylolisthesis seemed to benefit the most. Although people who did not have surgery reported some improvement 2 years into the study, those who had surgery seemed to be doing considerably better. Additionally, SPORT showed that combining two surgical procedures—decompressive laminectomy and fusion—did not help patients who had lumbar spinal stenosis without degenerative spondylolisthesis any more than decompressive laminectomy alone did. The findings regarding intervertebral disk herniation equally were meaningful. Two years after surgery, patients who had surgery for a herniated upper lumbar disk felt significantly better than those who had a lower disk repaired. Although more costly than nonoperative approaches, such as medications and physical therapy, lumbar discectomy is a cost-effective treatment, regardless of whether the damaged disk is in the upper or lower portion of the lumbar spine.

- Lurie JD, et al. *J Bone Joint Surg Am* 2008;90(9):1811-9. PMID: 18762639. PMCID: PMC2657310.
- Tosteson AN, et al. *Ann Intern Med* 2008;149(12):845-53. PMID: 19075203. PMCID: PMC2658642.
- Tosteson AN, et al. *Spine* 2008;33(19):2108-15. PMID: 18777603.
- Weinstein JN, et al. *Spine* 2008;33(25):2789-800. PMID: 19018250. PMCID: PMC2756172.
- Weinstein JN, et al. *N Engl J Med* 2007;356(22):2257-70. PMID: 17538085. PMCID: PMC2553804.
- Weinstein JN, et al. *N Engl J Med* 2008;358(8):794-810. PMID: 18287602. PMCID: PMC2576513.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIAMS, CDC/NIOSH, ORWH)

Bolstering the Research Continuum

Extramural Construction Program Expands Research Capacity: The American Recovery and Reinvestment Act (ARRA) provided \$1 billion to NIH for the Extramural Construction program. The program will build capacity to conduct biomedical and behavioral research by supporting the costs of improving non-Federal basic research, clinical research, and animal facilities to meet the research, research training, or research support needs of institutions. One component of the program, the Extramural Research Improvement Program, awards grants to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities for biomedical and behavioral research. Another component of the program, the Core Facility Renovation, Repair, and Improvement activity, awards grants to public and nonprofit private entities to renovate, repair, or improve core facilities. A core facility is a centralized shared resource that provides access to instruments or technologies or services, as well as expert consultation to investigators supported by the core. Institutions apply for construction grants by submitting applications, which are selected using NIH's standard, competitive, peer-reviewed process. Funding decisions are based on the scientific and technical merit of the application as determined by first and second level of peer review, the availability of funds, the relevance of the application to NIH program priorities, the national geographic distribution of awards, and the priorities specified in the ARRA, such as energy efficiency and job creation. The objective of the ARRA Extramural Construction program aligns with the objective of the existing Research Facilities Improvement Program, which is also administered by NIH.

- For more information, see <http://www.ncrr.nih.gov/recovery/construction>

- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E) (NCR) (ARRA)

ARRA-Funding Expands Research Capabilities: NCR is using its ARRA funds designated for scientific research to accelerate the Center's research priorities and support research, resources, tools, and training to help researchers funded by NIH transform basic discoveries into improved human health. In contrast to most of the NIH ICs that fund primarily Research Project Grants (i.e., R01s), NCR primarily supports large Center programs that build research capacity and offer training and career development. Consistent with NCR's research portfolio, a few previously reviewed Research Project Grants (R01s and R21s) are being awarded with ARRA funds. Through competitive revision awards, NCR is encouraging NIH-funded researchers (primarily supported by other NIH ICs) to leverage the resources, expertise, and infrastructure of NCR centers and Center-like programs. To further advance the scientific progress of NCR programs, administrative supplements are being awarded to: advance translational (pre- and post-clinical) research, achieve CTSA consortium strategic goals, enhance NCR pilot project mechanisms, promote collaborative community engagement research, improve research workforce development, and strengthen science education and dissemination. A new ARRA-supported initiative will develop infrastructure to connect people and resources across the Nation and promote interdisciplinary collaborations and scientific exchange. Additional ARRA funding is supporting NIH-led activities such as the Challenge Grants and the Summer Research Experiences for Students and Science Educators. From the beginning of the ARRA-funding strategy development, NCR leadership decided to align its ARRA activities broadly with the goals and objectives of the NCR 2009-2013 Strategic Plan.

- For more information, see <http://www.ncrr.nih.gov/recovery>
- For more information, see http://www.ncrr.nih.gov/strategic_plan/implementation/
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Technology Development*
- (E) (NCR) (ARRA)

Shared Instrumentation Grant and High-End Instrumentation Programs: The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the \$100,000-\$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the \$750,000-\$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located at core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2008, the SIG program funded a total of 82 grants for \$30,623,406; the HEI funded a total of 20 awards for \$33,309,434. In FY 2009, NIH received \$300 million in ARRA funding to provide shared instrumentation to extramural researchers through the SIG and HEI programs. To best serve the needs of NIH-supported investigators, the range of HEI awards funded by ARRA was expanded and now is \$600,000 to \$8 million.

- For more information, see <http://www.ncrr.nih.gov/btinstruments>
- For more information, see <http://www.ncrr.nih.gov/recovery>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E) (NCR) (ARRA)

Clinical and Translational Research

Using Systems Science Methodologies to Protect and Improve Population Health: Solutions to complex problems, such as chronic disease, require approaches that can address a broad range of factors within a single framework—from genetic to environmental, cellular to behavioral, and biological to social. In May 2007, NIH sponsored a conference, Complex Approaches to Population Health, at the University of Michigan. This well-attended (300 persons) conference brought computational/mathematical modelers together with behavioral and social scientists to discuss longstanding problems in health that might be addressed with these modeling methods. A primary purpose of the conference was to raise awareness of systems science methodologies as a means for addressing population health problems. Informed by the 2007 meeting, NIH issued the initiative PAR-08-224, Using Systems Science Methodologies to Protect and Improve Population Health, in August 2008. The initiative solicits R21 grant applications that propose using systems science methodologies to address policy resistant health problems. There are three application receipt dates per year through 2011.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-224.html>
- (E) (**OBSSR**, FIC, NCCAM, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIDCR, NIEHS, NIMH, ODP, ODP/ODS)

Blueprint Interdisciplinary Research Training: Under the auspices of the NIH Blueprint, interdisciplinary training programs have been established in computational neuroscience, neuroimaging, and translational research in the neurobiology of disease.

- The computational neuroscience programs seek to attract undergraduate and predoctoral students from the physical, mathematical, and engineering sciences to neuroscience research, and to expand the training of neuroscience students in quantitative sciences. Students learn how to develop models of neural systems or processes, test them experimentally, and then use experimental data to refine the models.
- The neuroimaging programs support predoctoral students and summer research intensives and provide comprehensive training in the breadth of imaging techniques and their application to neuroscientific questions. The goal of these programs is to train the next generation of neuroimaging researchers in the limitations, advantages, and underlying principles of currently available neuroimaging modalities.
- The translational research programs support students at multiple stages of their careers. The programs are designed to cross-train students in basic and clinical neuroscience, focusing not on specific diseases but on the biological mechanisms that are shared across diseases.

These Blueprint training programs are successfully seeding the field of neuroscience with highly qualified graduate students, postdoctoral fellows, and faculty.

- For more information, see http://neuroscienceblueprint.nih.gov/neuroscience_resources/training.htm
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Research Training and Career Development*
- (E) (**NIH Blueprint**, NCCAM, NCCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

Recruiting for HIV Research Using Mobile Vaccine Units: Evaluating the safety of candidate vaccines and treatments in humans depends on trust and partnership among scientists, clinicians, and study volunteers. NIH is reaching out to District of Columbia (DC)-area communities to raise awareness among diverse groups about HIV/AIDS. The mobile clinic is an extension of the vaccine clinic of the NIH Vaccine Research Center (VRC). The mobile clinic facilitates collaboration among scientists, clinicians, and study volunteers by raising awareness about HIV vaccines and by improving access for volunteers. With its new mobile clinic, the VRC enhances this vital collaboration by improving access for people in the DC metropolitan area who volunteer for clinical research studies to help find vaccines for HIV/AIDS and other infectious diseases. The mobile clinic can expand NIH outreach and recruitment efforts to neighborhoods in Baltimore and Frederick, Maryland, as well as DC and its suburban neighbors. The unit made its first

community appearance in June 15, 2008, at the 33rd annual Capital Pride Festival (a signature event held by the lesbian/gay/bisexual/transgender community).

- For more information, see http://nihrecord.od.nih.gov/newsletters/2008/07_25_2008/story4.htm
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (I) (NIAID)

Stimulating Transformative Research in HIV/AIDS: In recent years, widespread public education campaigns in the United States have fueled progress in reducing HIV/AIDS transmission that occurs through the sharing of injection equipment among drug users. However, transmission through high-risk sexual contact is on the rise—these behaviors often are exacerbated by substance abuse and ensuing altered judgment. To achieve a more comprehensive approach to this problem, NIH initiated its Avant-Garde Award series in 2008, with the goal of stimulating high-impact research from varied scientific disciplines to pave new avenues of treatment for HIV disease and prevention of new HIV infections among drug abusers. This award, modeled after NIH's Pioneer Award, provides funds of up \$0.5 million per year for 5 years and uses interviews with prospective candidates to more fully discern the scientist's and project's potential. One exemplary awardee is evaluating the effectiveness of expanding highly active antiretroviral treatment (HAART) coverage among injection drug users as a population-level HIV prevention strategy. A second is focusing on the ability of HIV to hijack key proteins involved in the regulation of host cell gene expression. A second initiative, the AIDS-Science Track Award for Research Transition (A-START), facilitates the entry of newly independent and early career investigators into the area of drug abuse and HIV/AIDS, an identified area of research need. Examples of projects supported through this mechanism include research on: (1) statistical models to explain ethnic disparities in HIV/AIDS among drug users, and (2) effects of morphine on immune responses to a candidate HIV vaccine in a primate model.

- For more information, see <http://www.cdc.gov/hiv/topics/surveillance/incidence.htm>
- For more information, see <http://www.drugabuse.gov/about/organization/arp>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIDA)

Institutional Development Award (IDeA) Program: The NIH IDeA program fosters health-related research and improves the competitiveness of investigators in 23 states and Puerto Rico with historically low NIH funding. The IDeA program supports multidisciplinary centers and statewide collaborative partnerships that increase institutions' capacity to conduct cutting-edge biomedical research. IDeA supports faculty development and enhancement of research infrastructure at institutions and also promotes collaborative community-based research, particularly in minority communities and other medically underserved communities where health disparities persist. The IDeA program supports the IDeANet initiative, which is expanding access to high-performance computational resources for data-intensive science applications and providing bioinformatics software tools and training to investigators. IDeANet began with the Lariat Networking Project, a pilot program that has enabled connectivity in six IDeA states in the Northwest (Alaska, Hawaii, Idaho, Montana, Nevada, and Wyoming) in partnership with the University of Washington and the University of California, San Diego. The Louisiana Optical Network Initiative (LONI) followed, supporting high bandwidth connectivity in Louisiana and Mississippi. Recently, five IDeA states have formed the North East Cyberinfrastructure Consortium (Delaware, Maine, New Hampshire, Rhode Island, and Vermont). IDeANet ultimately will enable all institutions in the IDeA program to engage in national and international collaborations.

- For more information, see <http://www.ncrr.nih.gov/riidea>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NCRR) (GPRA)

Clinical and Translational Research

Research Centers in Minority Institutions (RCMI): The RCMI program has developed and enhanced the research infrastructure of minority-serving institutions by expanding human and physical resources for conducting basic, clinical, and translational research. It began in 1985 in response to congressional report language (House Report 98-911, on the Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill for FY 1985; July 26, 1984; pages 78-79), directing funds to "establish research centers in those predominantly minority institutions which offer doctoral degrees in the health professions or the sciences related to health." The RCMI program has provided resources to acquire advanced instrumentation, renovate laboratory facilities, and improve research infrastructure. Additionally, it has enhanced faculty development, funded pilot projects, and supported core facilities. Because many RCMI investigators study diseases that disproportionately affect minorities, NIH support has brought more minority scientists into mainstream research and enhanced biomedical research focused on improving the health of racial and ethnic minorities and other medically underserved populations. The RCMI program includes various types of awards to help improve research capacity and reduce health disparities. For example, the RCMI Translational Research Network has fostered collaboration among researchers, developed and shared practices in disease prevention in local communities, and funded informatics tools for managing clinical research data. The RCMI program also has supported Clinical Research Education and Career Development awards that provide didactic training and mentor clinical research experiences to develop independent researchers.

- For more information, see <http://www.ncrr.nih.gov/rircmi>
- For more information, see <http://www.ncrr.nih.gov/rtrn>
- For more information, see <http://www.ncrr.nih.gov/crecd>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NCRR, NCMHD, NHLBI, NIA, NIAMS, NICHD, NIDA, NIDDK, NIMH)

Research Training and Career Development for Veterinarians in Translational Biomedical Research: Two recent reports from the National Academies, *National Need and Priorities for Veterinarians in Biomedical Research* and *Critical Needs for Research in Veterinary Science*, have confirmed the shortage of veterinarians involved in biomedical research. To address the shortage, NIH provides research training awards ("T" Awards) in biomedical research specifically for veterinarians and veterinary students. During FY 2008, more than 75 veterinarians received research training under the "T" mechanism. The mentored Career Development Awards ("K" Awards) to veterinarians serve as a bridge for postdoctoral fellows to become independent investigators. In FY 2008, 22 career development "K" awards were made to young veterinary investigators to increase the number of biomedical researchers with this expertise. Additionally, another initiative encourages the training of veterinarians in nonhuman primate clinical medicine at NIH-supported primate centers to address the shortage of clinical veterinary support for research primate colonies.

- For more information, see http://www.ncrr.nih.gov/career_development_opportunities/individual_training_grants/
- This example also appears in Chapter 3: *Research Training and Career Development*
- (E) (NCRR)

Center for Human Immunology, Autoimmunity, and Inflammation: The Center for Human Immunology, Autoimmunity, and Inflammation (CHI) is a new trans-NIH intramural initiative designed to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiology, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease. The Center provides unique specific technologies often unavailable to individual laboratories because of cost, complexity, and novelty. The core of CHI is made up of three technology centers. The first center features assays of immune cells and their products, based mainly on a technique known as flow cytometry and similar emerging techniques. The second center contains high-throughput systems technologies, involving the use of new methods for large-scale examination of genes, proteins, enzymes, and/or lipids. It also features advanced biostatistical

and computer modeling methods for mining these diverse data sets, thereby providing for a deeper understanding of immune function and pathology. The third center is based in protocol development, with staff dedicated to producing methods that efficiently translate to the clinic while considering all of the ethical and regulatory requirements for human research.

- For more information, see <http://www.nhlbi.nih.gov/resources/chi/index.htm>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Technology Development*
- (I) (NIAMS, NCI, NHLBI, NIAID, NICHD, NIDDK, NINDS)

Translational Research at the Aging/Cancer Interface: The NIH Translational Research at the Aging/Cancer Interface initiative was established in 2008 to enhance research in the overlapping areas of human aging and cancer by (1) integrating knowledge of basic processes in cancer biology and aging into clinical care of older patients with cancer ("bench to bedside"), and (2) exploring clinical observations from the patient care setting at more basic and molecular levels ("bedside to bench"). Research supported by this initiative holds potential for improving prevention, diagnosis, and disease management; improving the health and well-being of older adults at risk for or diagnosed with cancer; and decreasing the functional impairment and morbidity associated with cancer in this population.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-230.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-231.html>
- This example also appears in Chapter 2: *Cancer*
- (E) (NIA)

Public Trust Initiative: The NIH Public Trust Initiative (PTI), in partnership with the NIH Roadmap for Research, seeks to provide an inventory of activities that NIH and its individual Institutes and Centers are engaged in that involve public constituents, and that are intended to inform, educate, hear from, and serve the public. In 2008, NIH extended a new opportunity in community-based research under the PTI, the Partners in Research initiative (PIR). The PIR provides a unique opportunity for scientists to team up with community organizations to address the practical questions surrounding the development of true partnerships between researchers and the public. The goals of these partnerships are to: facilitate discussion of the health care needs and interests of the community; develop and implement research programs that address these needs; study methods to engage and inform the public regarding health science; improve public understanding of the benefits of publicly funded research; and communicate the results of this research. NIH received more than 200 applications in response to this opportunity, and a total of 37 projects were funded in 2008. On October 26-27, 2009, NIH convened a PIR workshop to examine the experiences of those participating in the PIR program. Participants discussed various aspects of the PIR program, including, for example, building partnerships, establishing criteria for a good partnership, and identifying challenges to this type of research.

- For more information, see <http://publictrust.nih.gov>
- (E) (NINR, NICHD, CC, FIC, NCI, NCCR, NIAID, NIDCR, NIGMS, OCPL, OIR, OSP/OBA)

Molecular Therapy Centers for Cystic Fibrosis and Other Genetic Metabolic Diseases: NIH is working to develop new approaches to treating serious, chronic, genetic diseases like cystic fibrosis and mucopolysaccharidosis. For example, the Gene Therapy and Cystic Fibrosis Centers Program currently supports Molecular Therapy Centers and a Cystic Fibrosis Research and Translation Core Center. Molecular Therapy Centers provide shared resources to a group of investigators to facilitate development of molecular therapies for the treatment of cystic fibrosis and other genetic metabolic diseases, like so-called lysosomal storage disorders such as mucopolysaccharidosis I. The Cystic Fibrosis Research and Translation Core Center provides resources and supports research on many aspects of the pathogenesis and treatment of cystic fibrosis. These centers have made important strides in recent years, including the study of promising

Clinical and Translational Research

candidate therapeutics. One of these, PTC124, is designed to overcome a mutation in the cystic fibrosis gene that otherwise yields a truncated, inactive cystic fibrosis protein. Other centers are screening libraries of compounds for other agents that might be safe and effective therapeutics for cystic fibrosis and other metabolic diseases.

- Du M, et al. *Proc Natl Acad Sci U S A* 2008;105(6):2064-9. PMID: 18272502. PMCID: PMC2538881. Galiotta LJV, et al. *FEBS Letters* 2001;499(3):220-4. PMID: 11423120.
- For more information, see <http://www2.niddk.nih.gov/Research/ScientificAreas/GeneticGeneTherapy/GCTR.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDDK)

Training Activities of the Clinical and Translational Science Award Program: Clinical research requires unique skills in addition to those needed to care for patients, so academic health centers must equip members of clinical research teams with the special training and experience they need to succeed. NIH expanded its clinical research training programs through Roadmap T32 and K12 programs that largely have been assimilated into Clinical and Translational Science Awards (CTSAs). Clinical research trainees learn the skills needed to cultivate multidisciplinary research team collaborations and design research projects to compete successfully for funding in a mentored environment. The CTSA training program already is providing more than 1,000 research training and career development opportunities in multiple individual disciplines. As mandated in Section 106 of the National Institutes of Health Reform Act of 2006 (Pub. L. No. 109-482), NIH will evaluate the outcomes and effectiveness of the CTSA training programs. The evaluation will include surveys of trainees, scholars, and mentors and will address pediatric clinical research training issues. In addition, the evaluation will conduct secondary analyses of pediatric clinical research training data collected by the CTSA program. This is part of a much larger comprehensive evaluation of the CTSA program as a whole. Each individual CTSA recipient also evaluates his or her own training activities, and the CTSA Education/Career Development Key Function Committee provides a forum in which best educational practices can be identified. The CTSA program was initiated in September 2006, so the long-term impact of the CTSA program will not be known for 7 or more years. However, short-term process milestones and intermediate outcomes are expected in 1 to 7 years. For example, the CTSA consortium defined training standards for core competencies in clinical and translational research. The consortium identified the skills, attitudes, and knowledge that investigators need to participate successfully in multidisciplinary teams of clinician-scientists.

- For more information, see <http://nihroadmap.nih.gov/clinicalresearch/overview-training.asp>
- For more information, see <http://www.ctsaweb.org>
- For more information, see <http://www.ncrr.nih.gov>
- This example also appears in Chapter 3: *Research Training and Career Development*
- (E) (NCRR, Common Fund - all ICs participate)

Interdisciplinary Research Consortia Funded by the NIH Roadmap: One of the four main initiatives established by the NIH Roadmap's Interdisciplinary Research Work Group was a grant program to fund large-scale consortia to support interdisciplinary research. In total, NIH funded nine collaborative teams located across the United States. Each focuses on a particular health problem or process, including substance abuse and stress; obesity; developmental disorders; the process of aging; providing fertility options for cancer survivors; engineering healthy tissue to treat diabetes, heart disease and oral/craniofacial disorders; psychiatric disorders; drug/medications development; and genome engineering. The initial results suggest ways in which this team science approach helps to increase cooperation within and between academic institutions, as well as advancing the individual missions of NIH ICs.

- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/>
- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp>
- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/members.asp>

- For more information, see <http://nihroadmap.nih.gov/>
- This example also appears in Chapter 3: *Technology Development*
- (E, O) (NIDCR)

Enhancing Behavioral and Social Sciences in Medical Education: In 2004, the Institute of Medicine (IOM) released its report on *Improving Medical Education: Enhancing the Behavioral and Social Science Content of Medical School Curricula*, which NIH funded. The report summarized how medical school curricula should be enhanced to address critical health issues faced in the United States today. One major finding was that approximately half of all causes of mortality in the United States are linked to social and behavioral factors such as smoking, diet, alcohol, sedentary lifestyle, and accidents. While generally it is recognized that biomedical research alone cannot address these issues, the IOM found that the curriculum in most U.S. medical schools does not provide sufficient teaching about these behavioral and social risk factors. In response to the IOM report, NIH issued a 2004 RFA and funded grants to nine medical schools to develop, pilot, and disseminate behavioral and social sciences modified curricula across the six domains identified by the IOM: (1) Mind-Body Interactions in Health and Disease, (2) Patient Behavior, (3) Physician Role and Behavior, (4) Physician-Patient Interactions, (5) Social and Cultural Issues in Health Care, and (6) Health Policy and Economics. Working in close collaboration, these medical schools are addressing how to incorporate behavioral and social sciences content throughout all 4 years of medical school in both the preclinical and clinical curricula. About 6,100 medical students will be affected by curricular innovations over the next 2 years of this 5-year collaborative effort.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-05-001.html>
- (E) (OBSSR, NCCAM, NCI, NHLBI, NIAMS, NICHD)

Clinical and Translational Science Award (CTSA) Program: The CTSA program is a partnership between NIH and a national consortium of 46 academic health centers and research institutions to build academic homes for clinical and translational research. By 2011, NIH expects to fund 60 CTSA institutions at a total cost of \$500 million per year. The CTSA program is designed to translate more efficiently the rapidly evolving knowledge developed in basic biomedical research into treatments to improve human health. The CTSA institutions are designing clinical and research informatics tools, forging new partnerships with private and public health care organizations, expanding outreach to minority and medically underserved communities, and developing better designs for clinical trials. Additionally, the CTSA are training the next generation of clinical and translational researchers to excel in interdisciplinary team science. Working together, the consortium is developing and disseminating best practices, policies, procedures, and other measures to advance collaborative clinical and translational research. At the same time, NIH is encouraging active collaboration among CTSA and other NIH-funded programs and investigators to leverage program resources and increase efficiencies. The CTSA program is the primary initiative for addressing the NIH Roadmap for Medical Research theme to Re-Engineer the Clinical Research Enterprise.

- For more information, see <http://www.ncrr.nih.gov/ctsa>
- For more information, see <http://www.ctsaweb.org>
- (E) (NCRR, Common Fund - all ICs participate)

Clinical and Translational Science Award (CTSA) Program Evaluation: NIH recognizes the importance of accountability and the need to evaluate and demonstrate progress toward meeting the ambitious goals of the CTSA program. For this reason, each CTSA grantee is required to conduct an institutional evaluation and to submit an annual status report to NIH. Institutional evaluators also participate in the CTSA consortium's Evaluation Key Function Committee, which provides an interactive forum to share and disseminate best practices and approaches to evaluating CTSA grantee programs. Additionally, NIH has hired external evaluators from Westat, a leading government services organization, to evaluate implementation of the CTSA program independently, to consider stakeholders' needs and

Clinical and Translational Research

perceptions, and to identify barriers to and facilitators of progress. As data are collected and as the program continues to mature, evaluation efforts will capture long-term outcomes and the impact the CTSA program has had on transforming the discipline of clinical and translational research. NIH will ensure that program findings and outcomes are disseminated to stakeholders, including researchers, advocacy groups, and Congress.

- For more information, see <http://www.ctsaweb.org>
- For more information, see http://www.ncrr.nih.gov/ctsa/progress_report_2009
- (E) (NCR, Common Fund - all ICs participate)

Clinical and Translational Science Award (CTSA) Program Progress: Launched in 2006, NIH has made significant progress in building a national consortium for clinical and translational research. Since 2008, 22 new CTSA joined the consortium, adding representation from eight new states, additional pediatric expertise, and greater informatics capabilities. At the national level, the CTSA consortium has identified five strategic goals: developing strategies and resources to move laboratory discoveries into early clinical testing (T1 translation), reducing complexities and improving ways clinical and translational research is conducted, enhancing training and career development of clinical and translational investigators, encouraging consortium-wide collaborations, and improving the health of communities across the nation—with an emphasis on community engagement and comparative effectiveness research. Working together, the consortium has made substantial progress in improving the management of clinical research, developing core competencies in clinical and translational science, and accelerating the dissemination of research findings into clinical practice. The momentum of the CTSA consortium continues to build as new connections are emerging rapidly within, across, and beyond the consortium. For example, CTSA are connecting with the following NIH-funded institutions: Emory University (Atlanta, Georgia) is partnering with Morehouse School of Medicine; Vanderbilt University (Nashville, Tennessee) is partnering with Meharry Medical College; and Weill Cornell Medical College (New York, New York) is partnering with Hunter College.

- For more information, see <http://www.ncrr.nih.gov>
- For more information, see <http://www.ctsaweb.org>
- For more information, see http://www.ncrr.nih.gov/ctsa/progress_report_2009
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NCR, Common Fund - all ICs participate)

Collaborative Community-Based Research: NIH is focusing on strategies and best practices for conducting collaborative community-based clinical and translational research, particularly in minority and other medically underserved communities where health disparities persist. Programs such as the Institutional Development Award (IDeA) are encouraging efforts to build and strengthen partnerships among government agencies, academic and private-sector organizations, community health providers, and organizations that also are working to improve community health outcomes. Translational, community-based research funded in several IDeA states, in both urban and rural settings, is focusing on:

- Enhancing recruitment and retention of research subjects through community buy-in
- Implementing practical and effective research protocols in community health care settings
- Developing versatile and sustainable core research infrastructure to encourage community participation and leverage existing resources

In addition, in FYs 2008 and 2009, NIH conducted workshops to gather specific recommendations from the community that are helping to shape future initiatives to enhance clinical and translational research in minority and other medically underserved communities. Workshop participants included other HHS-agencies such as AHRQ, CDC, the Indian Health Service, and HRSA.

- For more information, see http://www.ncrr.nih.gov/research_infrastructure
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NCRR)

Community-Based Participatory Research (CBPR): CBPR is an orientation to research that requires a collaborative approach to involve community stakeholders throughout all stages of research projects. This community input offers CBPR the potential to generate better-informed hypotheses, develop more effective interventions, and enhance the translation of research results into practice. NIH issued three funding opportunity announcements (FOAs) on CBPR in January 2008. One FOA, Community Participation in Research, solicits jointly conducted intervention research. The remaining FOAs, Community Participation Research Targeting the Medically Underserved, solicit jointly conducted research in medically underserved areas/populations; all three FOAs focus on health promotion, disease prevention, and health disparities. A corresponding technical assistance workshop, Leap into the Community, convened February 2008 and offered comprehensive instruction from NIH program and review officials on the CBPR approach and preparing responsive applications to the FOAs. Outreach and training activities on CBPR have included the creation of an educational brochure (November 2007); organization of two special sessions at annual scientific meetings for the Society of Behavioral Medicine and the American Sociological Association on the principles and efficacy of CBPR and showcasing successful NIH-funded research projects (March 2008 and August 2009, respectively); and planning of the 2009 NIH Summer Institute on Community-Based Participatory Research Targeting the Medically Underserved, which addresses essential issues inherent in conducting community-partnered research with medically underserved areas/populations (August 2009).

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-074.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-075.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-076.html>
- For more information, see http://obsr.od.nih.gov/scientific_areas/methodology/community_based_participatory_research/CBPR_TA_WrksHp.aspx
- For more information, see http://obsr.od.nih.gov/scientific_areas/methodology/community_based_participatory_research/CBPR_ASA.aspx
- For more information, see <http://conferences.thehillgroup.com/si2009/index.html>
- For more information, see http://obsr.od.nih.gov/scientific_areas/methodology/community_based_participatory_research/index.aspx
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (OBSSR, CDC/NIOSH, NCI, NHLBI, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINR, ORWH)

Community Participation in Health Disparities Intervention Research Program: NIH supports the development, implementation, and evaluation of intervention research by using community-based participatory research (CBPR) principles and methods in targeting diseases of major public health importance in health disparity communities. This unique multiyear CBPR initiative promotes participatory research collaborations between scientific researchers and their community partners and will engage communities in all stages of the research process for a total of 11 years (3-year planning phase, 5-year intervention phase, and 3-year dissemination phase). The participatory partnerships formed between researchers and the community are expected to (1) transform the research questions from researcher to community-centered; (2) focus the research area, strategies, and methods to address those diseases and conditions of highest community interest and need; and (3) accelerate the identification and testing of interventions that are likely to make the largest difference in the health of the community. The CBPR initiative began in FY 2005 with the award of 25 3-year research planning grants. CBPR planning grantees conducted needs assessments, focus groups, and pilot intervention studies for addressing health disparities among health disparity populations in 20 states. In FY 2008, 40 5-year

Clinical and Translational Research

intervention research grants focusing on diabetes, cancer, cardiovascular disease, substance abuse, and other diseases and conditions were awarded. This intervention phase will be followed by a competition for 3-year dissemination grants to be awarded in FY 2013. In May 2009, RFA MD-09-006, "Recovery Act Limited Competition: NCMHD Community Participation in Health Disparities Intervention Research Planning Phase," was issued for a 2-year planning research phase. Awards for this phase were made in FY 2009. Current CBPR pilot intervention research studies include:

- Suicide and alcohol use prevention among Alaska Native youth living in five communities in Alaska
- HIV/AIDS prevention among African Americans in North Carolina
- Obesity prevention using individual, family, and community-level interventions among Native Hawaiian and Pacific Islanders in Hawaii
- Diabetes prevention among Hispanic communities in border areas in Texas
- Hypertension prevention among Filipino Americans in New York City and New Jersey
- Cancer prevention among low-income Appalachian communities in Ohio by increasing colorectal cancer screening

→ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/rfa-md-07-003.html>

→ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-09-006.html>

→ This example also appears in Chapter 2: *Minority Health and Health Disparities*

→ (E) (NCMHD)

Testing for Reproductive Tumors in the National Toxicology Program's Carcinogenesis Bioassay: Perinatal

Dosing: The National Toxicology Program (NTP) evaluates substances for a variety of health-related effects. Two-year studies in laboratory rodents remain the primary method by which chemicals or physical agents are identified as having the potential to be hazardous to humans. In 2006, NTP convened a workshop on Hormonally Induced Reproductive Tumors, Relevance of Rodent Bioassays to discuss the adequacy of rodent models used in the 2-year bioassay for detecting reproductive tumors. The workshop recommended that in utero and lactational exposures could be added to the chronic bioassay depending upon what is known about the mode of action. For detecting tumor types such as testicular germ cell tumors, this recommendation was especially strong. In utero and lactational exposures should be considered for mammary tumor studies if there are any developmental effects associated with a substance under study that involved endocrine tissues, steroid receptor binding, a change in mammary gland morphology, or altered timing of vaginal opening. NTP has conducted such perinatal exposures on cancer bioassays in the past, but only when there was special justification for such a design to be adopted. A new default design in which dosing will start in pregnancy and be continued throughout life or to the end of a 2-year period now has been adopted unless there is a good scientific reason not to undertake such a study. NTP has initiated studies to obtain data for constructing physiologically based pharmacokinetic (PBPK) models in rodents and nonhuman primates. It is planning studies to explore the long-term consequences of perinatal exposure to Bisphenol A to understand the potential impact to humans of the developmental changes reported in numerous laboratory animal studies. It is hoped that the PBPK models will link information from rodent studies with primate studies, and potentially with human outcomes.

→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*

→ (O) (NIEHS)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists,

research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects adipose tissue and alters hormonal control of sexual maturation. Endocrine disruptors, irradiation, and psychosocial elements also will be studied for effects.

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- For more information, see <http://www.bccrc.org/>
- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIEHS, NCI) (GPRA)

Cancer Health Disparities Research Programs and Initiatives: NIH has expanded research on the basic biologic factors of cancer disparities to provide a foundation for minimizing risk, identifying targets, developing preventive and therapeutic interventions, and understanding how genetic susceptibility may be influenced by social, economic, race/ethnicity, and geographic factors. Thus, the research programs involve multidisciplinary teams, which contribute to understanding the etiology of cancer and build prevention and intervention evidence-based models to eliminate cancer disparities. Several programs at NIH address disparities along the cancer continuum from prevention to survival.

- The trans-disciplinary Geographic Management Program (GMAP) pilot initiative builds regional networks to support research, training, and infrastructure to develop state-of-the-art networks/centers to ensure a continuous supply of high-quality human biospecimens from multi-ethnic communities.

Clinical and Translational Research

- The Community Networks Program engages communities experiencing cancer disparities to design, test, and evaluate evidence-based strategies to address critical needs, such as access to screening, mentoring, and training; policy development; and community outreach and education.
- The Patient Navigation Research Program builds partnerships to ensure that racial/ethnic minorities and underserved populations with abnormal cancer screening results receive appropriate care.
- The Community Clinical Oncology Program is a network for conducting cancer prevention and treatment clinical trials by connecting academic centers with community physicians.
- The NIH Centers for Population Health and Health Disparities catalyze transdisciplinary research to improve the understanding of complex interactions of biological, social, cultural, environmental, and behavioral factors that contribute to health inequities, and to develop and implement novel intervention strategies that are multilevel and multifactorial.
- The Tobacco Research Network on Disparities' mission is to understand and address tobacco-related disparities by advancing the science, translating that scientific knowledge into practice, and informing public policy.
- The Centers of Excellence in Cancer Communication Research continue to use best practices in communication science to extend the reach of biomedical benefits equitably throughout the population.

→ For more information, see <http://crchd.cancer.gov/>

→ For more information, see <http://crchd.cancer.gov/cnp/background.html>

→ For more information, see <http://crchd.cancer.gov/pnp/pnnp-index.html>

→ For more information, see <http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html>

→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Molecular Biology and Basic Research*

→ (E) (NCI)

Collaborations Between Minority-Serving Institutions and Cancer Centers: The Minority Institution (MI)/Cancer Center (CC) Partnership (MI/CCP) is a flagship program that has been instrumental in establishing strong collaborations between minority-serving institutions (MSIs) and CCs. MI/CCP has fostered strong cancer research partnerships throughout the United States. This program established new cancer research curricula, recruited new faculty, increased awareness about health care disparities and cultural sensitivities, and developed programs and outreach efforts in educating underserved communities. The MI/CCP has provided research education and training to individuals at all levels including postdoctoral fellows, medical students, graduate students, students at master's level, and baccalaureate and high school students. Establishing new collaborations and partnerships in communities has been a hallmark of this program, culminating in increases in numbers of awarded grant applications and numbers of manuscripts, oral presentations, and poster presentations at both regional and national levels. Many research advances are emerging from the Partnership. For example, through the Morehouse School of Medicine and University of Alabama Partnership, researchers have identified a possible genetic cause for increased risk for a more advanced form of colorectal cancer in blacks that leads to shorter survival. Understanding the relationship between molecular defects and differences in colorectal cancer incidence, aggressiveness, and clinical outcomes is important in individualizing the treatment and in eliminating racial disparities.

→ For more information, see <http://crchd.cancer.gov/research/miccp-overview.html>

→ For more information, see <http://clincancerres.aacrjournals.org/cgi/content/full/15/7/2406>

→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Molecular Biology and Basic Research*

→ (E) (NCI)

Ethical, Legal, and Social Implications (ELSI) Centers of Excellence: NHGRI's ELSI program has established a network of Centers of Excellence in ELSI Research. Currently, four full Centers and three exploratory Centers are bringing together investigators of diverse expertise to investigate issues related to:

- Intellectual property of genetic information
- Translation of genetic information to health care
- Genetic research that involves human participants
- Use of genetic information and technologies in non-health care settings, such as employment, insurance, education, criminal justice, or civil litigation
- Impact of genomics on the concepts of race, ethnicity, and individual and/or group identity
- Implications of uncovering genomic contributions to human traits and behaviors, such as aging or addictions
- How different individuals, cultures, and religious traditions view the ethical boundaries for the uses of genomics

→ For more information, see <http://www.genome.gov/10001618>

→ This example also appears in Chapter 3: *Genomics*

→ (E) (NHGRI)

Advancing Novel Science in Women's Health Research (ANSWHR): A trans-NIH grants program, ANSWHR, is encouraging innovative, interdisciplinary research that promotes new concepts in women's health research and the study of sex/gender differences. Grants have been funded in areas such as genetic pathways in systemic lupus erythematosus (Lupus), sex differences in stress, sex differences relating to the vulnerability to cocaine addiction, inflammation and insulin sensitivity in obese pregnant women, novel ovarian cancer detection agents, evaluation of diagnostic techniques for cardiovascular events, sex differences in HIV/AIDS antiretroviral treatment, and sex differences and cognitive function. Based on responses to this program, ANSWHR is becoming an important scientific program that is enabling both early-stage investigators and veteran researchers to test nascent scientific concepts.

→ For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAS-07-381.html>

→ For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAS-07-382.html>

→ (E) (ORWH, FIC, NCI, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM, OBSSR, ODP/ODS)

Research Enhancement Awards Program (REAP): REAP increases the number of new research studies of women's health and/or the study of sex and gender factors by collaborating with the NIH ICs to identify and co-fund meritorious research grants that have just missed the cutoff for funding. Examples of scientific areas funded through this mechanism included breast reconstruction, estrogen effects on wasting of skeletal muscle, activin target genes in the regulation of ovarian follicle development, and improving contraceptive use and reducing unintended pregnancy rates among young low-income women.

→ For more information, see <http://orwh.od.nih.gov/research/recap.html>

→ (E) (ORWH, NCCAM, NCI, NIAMS, NICHD, NIDCR, NINDS)

Centers of Research Translation (CORT): The NIH CORTs are designed to bring together basic and clinical research to translate basic discoveries into new drugs, treatments, and diagnostics. Each CORT encompasses at least three projects, including one clinical and one basic research study. The centers are:

- The Center for Translating Molecular Signal Pathways to Orthopaedic Trauma Care studies the biological basis of fracture healing and the efficacy of a potential new treatment, teriparatide, an injectable form of human parathyroid hormone that stimulates new bone formation.
- The Center for Lupus Research investigates the role of different cell types in the origin and development of lupus, markers of disease activity and severity, and new targets for treatment.
- The Center for X-Linked Hypophosphatemic Rickets Research focuses on the various molecular contributors to this genetic form of rickets, and works toward developing new treatments.

Clinical and Translational Research

- The Center for Research Translation in Scleroderma is studying the molecular basis of scleroderma to understand its underlying causes, using functional genomics and gene networks.
- The Center for Genetic Dissection of Systemic Lupus Erythematosus (lupus) studies mouse models of lupus to identify the genetic background of developmental stages of the disease.
- The Center for New Approaches to Assess and Forestall Osteoarthritis in Injured Joints is developing new methods of forestalling post-traumatic osteoarthritis (PTOA).
- The Center for Psoriasis Research Translation uses a Phase I mechanistic, safety, and preliminary efficacy study to test a novel photodynamic therapy for psoriasis.

→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/11_08.asp

→ For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2007/corts.asp

→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 2: *Minority Health and Health Disparities*

→ (E) (NIAMS)

Improving Research Efficiency

2009 Institute of Medicine Report, The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors:

The recently released IOM report, *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*, reviews U.S. interest and investment in global health. This report is particularly timely and useful given the major changes in global health that have occurred since the last IOM report, *America's Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests*, was released in 1997. These changes include unprecedented interest and large fiscal commitments to global health by the U.S. government and nongovernmental sectors. The IOM leveraged the contributions of 18 NIH ICs to undertake this update with additional financial support from several key private and public entities. The study makes the case for why U.S. agencies and private sector entities should invest more heavily in global health. The report has five key recommendations that can inform NIH investments in global health in the coming years:

- Scale up existing interventions to achieve significant health gains
- Generate and share knowledge to address health problems endemic to the global poor
- Invest in people, institutions, and capacity-building with global partners
- Increase U.S. financial commitments to global health
- Set the example of engaging in respectful partnerships

The IOM panel was chaired by Dr. Harold Varmus and Ambassador Thomas Pickering. A preliminary report, titled *The U.S. Commitment to Global Health: Recommendations for the New Administration*, was released in December 2008. In May 2009, the final report, titled *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*, was released.

→ For more information, see <http://www.iom.edu/Reports/2009/The-US-Commitment-to-Global-Health-Recommendations-for-the-Public-and-Private-Sectors.aspx>

→ For more information, see <http://www.iom.edu/Reports/2008/The-US-Commitment-to-Global-Health-Recommendations-for-the-New-Administration.aspx>

→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Chronic Diseases and Organ Systems*

→ (O) (FIC, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS)

Harmonization of Adverse Event Reporting, Analysis, and Communication: Clinical Research Policy Analysis and Harmonization (CRpac) has led a major effort to improve understanding and compliance with adverse event reporting requirements and to standardize the reporting of adverse event data. An interagency task force, the Federal Adverse Event Task Force (FAET), has been conducting a comprehensive assessment and analysis of existing Federal policies to identify opportunities for greater harmonization in reporting, analyzing, and communicating adverse events in research. The task force, which includes NIH, FDA, OHRP, CDC, AHRQ, VA, and DOD, has developed a core adverse event report that investigators can send to multiple agencies and develop best practices for reporting, analysis, and application of safety information. In addition, FAET has developed a Basal Adverse Event Report (BAER) that provides a single baseline set of information for reporting adverse events and unanticipated problems that is acceptable to multiple Federal agencies. It includes data elements needed for adverse event and unanticipated event reporting across all types of clinical research including behavioral, social science, epidemiologic, and surveillance studies. As a next step, a Web-based portal is under development to provide a seamless online method to submit adverse event reports. The goal is to develop a user-friendly electronic submission system to report an adverse event to NIH, FDA, and other government agencies from investigators, sponsors, physicians, and the public.

- For more information, see http://oba.od.nih.gov/policy/policy_issues.html#CRP_001
- (O) (OSP/OBA, Common Fund - all ICs participate)

Clinical and Translational Research

⁴⁸ CDC Diabetes Fact Sheet. 2007. For more information, see: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf.

⁴⁹ World Health Organization. Diabetes Fact Sheet. <http://www.who.int/mediacentre/factsheets/fs312/en/index.html>. Accessed 6 August 2009. Geneva, Switzerland: WHO.

⁵⁰ Perreault L, et al. *Diabetes Care* 2009;32(9):1583-8. PMID: 19587364. PMCID: PMC2732165.

⁵¹ Knowler WC, et al. *N Engl J Med* 2002;346(6):393-403. PMID: 11832527. PMCID: PMC1370926.

⁵² Ackermann RT, et al. *Am J Prev Med* 2008;35(4):357-363. PMID: 18779029. PMCID: PMC2610485.

⁵³ Yang SH, et al. *Nature* 2008;453(7197):921-4. PMID: 18488016. PMCID: PMC2652570.

⁵⁴ As required by the NIH Reform Act of 2006, NIH provides an annual report to the U.S. Food and Drug Administration identifying all trials registered in www.clinicaltrials.gov.

⁵⁵ Federal Coordinating Council on Comparative Effectiveness Research. Report to the President and the Congress. June 30, 2009. Washington, D.C.: U.S. Department of Health and Human Services. p. 16.

⁵⁶ Federal Coordinating Council on Comparative Effectiveness Research. Report to the President and the Congress. June 30, 2009. Washington, D.C.: U.S. Department of Health and Human Services. p. 4.

Disease Registries, Databases, and Biomedical Information Systems

Disease Registries, Databases, and Biomedical Information Systems

Dr. Mark S. Drapkin, Chief, Infectious Disease Service at Newton-Wellesley Hospital (Newton, MA), was treating a 14-year-old girl diagnosed with the fulminant form of meningococemia. She was delirious and drifting into shock, and death was a real possibility. Specialist colleagues had no suggestions for new treatment approaches. Although the hospital library was closed for the night, Dr. Drapkin had it opened and did a quick Medline search. The search turned up an article in a British journal that suggested plasmapheresis, a procedure designed to remove excess antibodies from the blood by depleting the body of blood plasma without depleting its blood cells. Using the information from the article, Dr. Drapkin and his colleagues successfully treated the patient. "I would never have found these articles in the limited time frame under which we were working without an electronic search of the literature," said Dr. Drapkin.

Introduction

In a world that is increasingly digital, NIH plays a pivotal role in enabling biomedical research, improving health care and public health, and promoting healthy behavior. By connecting and making the results of research—from scientific data to published literature to patient and consumer health information—readily available, NIH magnifies the positive impact of the Nation's investment in the creation of new knowledge in the pursuit of improved health.

Information has become a primary driver of progress in biomedical research and the health care enterprise. For example, genomic data resulting from sequencing the genes of thousands of patients have become primary resources for identifying the genetic basis of diseases. Data that flow from large-scale clinical studies, advanced diagnostic and imaging equipment, and electronic health records are a key enabler of improvements in clinical practice and individual patient care. Up-to-date information from disease registries has become a critical resource for studying disease incidence and treatment patterns, advancing research, and informing public health interventions. The availability of this and other health information available on the Internet offers consumers a more active role in managing their health and further increases demand for reliable and authoritative health information.

The development, deployment, and utilization of disease registries, databases, and other biomedical information systems are essential to managing large amounts of data for research, clinical care, and public health. Such systems permit the efficient collection, organization, storage, sharing, and accessing of biomedical information. Today's biomedical databases house a wide range of clinical, genomic, and other types of scientific data and information resulting from biomedical research and make it accessible for further research or application. Disease registries collect information on cohorts of patients with specific diseases (e.g., cancer, autoimmune disorders, or Parkinson's disease) or who have received specific treatments (e.g., medical devices). They provide a rich source of information that is used by researchers, clinicians, and policymakers.

Increasingly, disease registries and biomedical databases serve not only as repositories of information, but also as research tools in and of themselves, extending and in some cases augmenting the laboratory. Discoveries can be made by examining the information contained in them. For example, scientists can use molecular databases to study the profiles of individual tumors and conceptualize small-molecule anticancer agents to target them. They can analyze large-scale databases linking genotype and phenotype information from thousands of individuals to identify genes associated with particular observable traits (e.g., obesity) or diseases (e.g., diabetes, cancer). In these ways, biomedical information systems are changing the nature of research itself, and promise to change the nature of clinical care and public health.

The utility of disease registries, databases, and biomedical information systems rests on many factors, including data quality, user accessibility, ease of search capability, availability of useful tools for analysis, and their ability to interoperate

with other systems. New data must be added on a regular basis, while existing data are maintained or updated to reflect new findings. Improved search tools are needed to comb through the massive datasets and retrieve relevant results. Standard vocabularies are needed to efficiently organize information, facilitate effective linking and sharing of information, and ensure accurate retrieval, and they, too, must be updated to accommodate new concepts and relationships. New analytical tools are needed to explore increasingly complex questions, such as how the expression patterns of multiple genes are associated with a particular trait or response. Such tools are most effective when information systems are interoperable and can communicate, exchange data, and make use of similar software applications. Given the critical importance of data to biomedical research and health care, policies and procedures are needed to encourage researchers to submit relevant data and to provide other researchers, clinicians, and the general public with suitable access to the data, while simultaneously protecting the confidentiality of personally identifiable information. Preserving, protecting, and ensuring the validity and security of information stored in biomedical databases remains of paramount importance.

Because of the growing importance of information and its management in biomedical science, clinical care, and public health, virtually every NIH IC is engaged in the development, deployment, and use of biomedical information systems that support its mission.

Because of the growing importance of information and its management in biomedical science, clinical care, and public health, virtually every NIH IC is engaged in the development, deployment, and use of biomedical information systems that support its mission. NIH databases and information systems have become indispensable national and international resources for biomedical research and public health. Several trans-NIH activities feature the development of significant biomedical information resources, including the tools, infrastructure, and associated research needed to make databases and registries more valuable. Many of the challenge grants supported with funds from the American Recovery and Reinvestment Act of 2009 (ARRA) relate to data systems and tools, focusing on a wide variety of informatics topics such as new computational and statistical methods for the analysis of large datasets from genome-wide association studies (GWAS) and the use of next-generation sequencing technologies, intelligent search tools for answering clinical questions, and new information technology and resources for disease prevention and personalized medicine.

This section of the Biennial Report describes NIH efforts to develop and deploy disease registries, databases, and biomedical information systems to advance biomedical science, health, and health care. It focuses on:

- **Scientific Databases.** These databases archive and provide access to authoritative scientific literature, essential research data (including disease-specific data), and clinical research information.
- **Genomic Information Systems.** Major systems include GenBank for genomic sequence data and dbGaP (database of Genotype and Phenotype) for GWAS data.
- **Disease Registries and Surveillance Systems.** NIH works with other Federal and private entities to integrate disease registries for national and local use. For example, the Surveillance, Epidemiology, and End Results (SEER) program has been the foundation for innumerable studies, including recent research into links between hormone therapy and breast cancer.

Emphasis is placed on intramural and extramural activities in which development and maintenance of such information resources is a primary objective, rather than a means of achieving another objective. The described disease registries, databases, and biomedical information systems are intended for widespread use by researchers, clinicians, public health officials, or the general public, and some are associated with policies that require or encourage the submission of particular data or information.

This section of the Biennial Report also describes NIH efforts to make these and other data systems more useful to researchers, clinicians, and the public. Of particular interest are activities related to the following:

Disease Registries, Databases, and Biomedical Information Systems

- Standardized Vocabularies and Data Protocols. NIH leads the government's efforts to develop standardized vocabularies and terminology to support interoperability among biomedical information systems in research and clinical settings.
- Large-Scale Informatics Infrastructure. NIH funds the development of large-scale systems and tools that allow communities of researchers to collect, share, and analyze data needed for research, clinical care (including electronic health records), and public health.
- Biomedical Informatics Research and Training. NIH is the largest Federal funder of biomedical informatics research, which aims to advance the applications of computing to biomedicine for both research and clinical care. Grant programs support research and training in medical informatics and medical librarianship.

Recent developments in policies and procedures to encourage the submission of data to NIH's disease registries, databases, and biomedical information systems also are reviewed.

Catalog of Disease Registry, Database, and Biomedical Information System Activities

In response to the mandate under SEC. 403 (a)(4)(C)(ii) of the Public Health Service Act to provide catalogs of disease registries and other data systems, included here is a live link to an inventory of NIH intramural and extramural activities ongoing in FYs 2008 and 2009 to develop or maintain databases, disease registries, and other information resources for the benefit of the larger research community. Based on a future assessment of the information collected in the inventory, NIH potentially may develop capacity to integrate this catalog as a new category within the NIH RCDC process.

Summary of NIH Activities

NIH Scientific Databases: Enhancing Access to Research Information

Keeping pace with the expanding volume of biomedical knowledge is a continuing challenge for scientists, clinicians, policymakers, and the public; thus, NIH devotes considerable attention and resources to developing, expanding, and maintaining tools and resources for information management. Biomedical databases store and provide access to a wide range of information, from the results of scientific or clinical research studies, to genomic information, to standard reference materials (such as genome sequences or anatomical images), to published journal articles and citations to the medical literature. They are widely used by biomedical researchers, as well as by a growing number of clinicians, public health officials, and consumers. NIH often undertakes special initiatives to make these resources more accessible to a broader, more diverse set of users.

Among the most widely used of NIH's databases are those that collect and provide access to **scientific literature**. These comprehensive resources are extensively used by scientists, health care providers, and consumers who seek trusted, peer-reviewed information on biomedical and health topics of interest. NIH houses the leading source of authoritative biomedical literature for professional and lay audiences. NIH's exhaustive PubMed/MEDLINE database, for example, indexes citations to articles in more than 5,300 peer-reviewed scientific journals. It contains references to more than 16 million journal articles in the life sciences, and 1.4 million new citations were added to the system during the 2-year period from FY 2008 to FY 2009. During the FY 2008-2009 biennial period, PubMed logged more than 1.5 billion Web-based searches.

The PubMed/MEDLINE database indexes citations to articles in more than 5,300 peer-reviewed scientific journals and contains references to more than 16 million journal articles in the life sciences. Almost 1.4 million new citations were added to the system during the 2-year period from FY 2008 to FY 2009.

In addition, NIH continues to expand PubMed Central (PMC), its digital archive of full-text scientific journal articles. PMC was established to provide online access to a growing number of scientific journal articles deposited by publishers and NIH-funded researchers. Between February 2007 and September 2009, the number of articles available in PMC

doubled to 1.9 million and usage rose by more than 60 percent to 360,000 users per day. Some of this increase is attributable to an expanding scope of users—not just biomedical researchers, but also clinicians, other practitioners, and consumers—which highlights the importance of this type of resource.

PMC serves as the repository for manuscripts submitted in accordance with the NIH Public Access Policy, which became mandatory in 2008. The policy ensures that the public and the scientific community have access to the published results of NIH-funded research by requiring NIH-funded scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to PMC. Manuscripts are to be submitted upon acceptance for publication and made accessible to the public no later than 12 months after publication. PMC software also is used by funding agencies in other countries to establish repositories for their funded research. The Wellcome Trust and other major research funders in the United Kingdom established a site that has been operational since 2008, and in 2009, NIH partnered with the Canadian Institutes of Health Research and the National Research Council's Canada Institute for Scientific and Technical Information to establish PMC Canada.

To further facilitate rapid access to emerging scientific findings, NIH announced in August 2009 the introduction of Rapid Research Notes (RRN), a resource to archive research results made available through online venues for rapid scientific communication. The RRN archive allows users to access research that is provided through participating publisher programs for immediate communication. Creation of such an archive had been discussed for many years, but the outbreak of 2009 H1N1 influenza in the spring of 2009 provided increased impetus for the project. The first collection to be archived in RRN will be an open-access, online resource for immediate communication and discussion of new scientific data, analyses, and ideas in the area of influenza. NIH expects the RRN archive to expand over time to include additional collections in other high-interest biomedical fields.

To further facilitate rapid access to emerging scientific findings, NIH announced in August 2009 the introduction of Rapid Research Notes, a resource to archive research results made available through online venues for rapid scientific communication.

NIH actively endeavors to make its information resources more accessible to varied types of users, as illustrated by its work on MedlinePlus, NIH's comprehensive health information source for consumers and health professionals. Another information source that is directed at a wide variety of users is Genetics Home Reference, NIH's website for consumer-friendly health information on genetic conditions. This information resource bridges consumer health information and scientific bioinformatics data and links to many existing resources at NIH and at other reliable sites.

NIH also puts effort into developing and maintaining information systems that collect data stemming from **biomedical research**, organize it, and make it accessible for subsequent research. NIH's PubChem database, for example, houses data flowing from the high-throughput bioassay centers that were established with NIH funding under the Molecular Libraries Initiative of the NIH Roadmap. It provides information about the biological activity of small molecules, organized as three linked databases along with a chemical structure similarity search tool. The number of unique compounds represented in PubChem more than doubled during FYs 2008-2009 from approximately 10 million to more than 25 million, while the number of bioassays rose from 600 to 1,700. As a result, PubChem provides bioactivity results from more than 50 million tests of small molecules. The number of users per day also increased from approximately 30,000 to 50,000. PubChem is integrated with NIH's Entrez suite of biomedical information resources, enabling users to retrieve related data from multiple databases and navigate among them with relative ease.

NIH is one of three Federal agencies to fund the Protein Data Bank (PDB), an archive of information about experimentally determined structures of proteins, nucleic acids, and complex assemblies. Information on more than 13,000 structures was added to the PDB in FYs 2008-2009, bringing its total content to more than 60,000 molecules. PDB allows users to search for molecules based on their sequence, structure, or function and provides tools to visualize and analyze downloaded structures.

Disease Registries, Databases, and Biomedical Information Systems

TOXNET is a cluster of 13 large databases covering toxicology, hazardous chemicals, environmental health, and related topics. TOXNET includes literature-based and research databases. It has been used by toxicologists for decades, assisting them in locating toxicology data, literature references, and toxic release information on particular chemicals, as well as in identifying chemicals that cause specific health effects. Peer-reviewed studies from the National Toxicology Program are used by State, local, and Federal health officials to assess the toxicologic potential of environmental compounds to cause adverse health effects such as cancer. To make the Hazardous Substances Data Bank component of TOXNET more useful to first responders at the scene of a disaster, NIH developed WISER, the Wireless Information System for Emergency Responders, which enables wireless access to a selection of the most relevant data for emergency responders. WISER can be installed on personal digital assistants, providing emergency personnel with access to critical information for identifying and safely cleaning up spilled chemicals, understanding their health effects, treating exposed victims, and assessing environmental impact.

To make the Hazardous Substances Data Bank component of TOXNET more useful to first responders at the scene of a disaster, NIH developed WISER, the Wireless Information System for Emergency Responders, which enables wireless access to a selection of the most relevant data for emergency responders.

NIH launched the National Database for Autism Research (NDAR) in FY 2009 as a repository for human subjects data stemming from autism research. NDAR hosts genetic, imaging, and phenotypic research data related to autism and makes it accessible to qualified researchers. The system provides researchers with standards to enable them to analyze and compare data from multiple research sites and different bioinformatics systems. It also offers bioinformatics tools for depositing, validating, and searching for information. Its collaboration mechanisms allow for sharing quality research data within the autism research community. NIH-funded researchers are strongly encouraged to share their data with NDAR to enable secondary use and analysis.

Another group of NIH-supported databases organize and provide access to **clinical research information**. NIH's ClinicalTrials.gov database was significantly enhanced during FYs 2008 and 2009 to respond to the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85), which expands the types of clinical trials that must be registered in ClinicalTrials.gov, increases the amount of information that must be submitted for each trial, and requires the submission of summary results data, including adverse events. During FYs 2008 and 2009, more than 34,000 trials were registered with ClinicalTrials.gov, raising the total number of registered trials in the system to 80,000. During that same time period, summary results of more than 830 trials were submitted to the system and made available to the research community and the general public.

In addition, the NIH Biomedical Translational Research Information System (BTRIS), which was initiated in 2008, was made available to the intramural NIH community in 2009. BTRIS is a powerful new tool for NIH investigators to access clinical research data, develop streamlined mechanisms for protocol reporting and data analysis, and reuse data for hypothesis generation and collaboration. New functionality will continue to be added to the system.

ProtoType is an assisted protocol authoring tool that provides a systematic framework where research protocols can be developed and maintained throughout their life cycle. ProtoType includes fully customized documents tailored toward individual Institutional Review Boards, allowing investigators to focus on the substance of their protocols, rather than the formatting.

Genomic Information Systems: Understanding the Genetic Basis of Disease

NIH also has made great strides in developing information resources to support genetics research. NIH has long supported genetics research through widely used resources such as GenBank, the NIH genetic sequence database. In FY 2009, NIH launched the Sequence Read Archive (SRA) to accommodate the massive quantities of data coming from sequencing projects that are using new high-throughput technologies. SRA is proving to be one of the fastest growing biological

databases in history, with more than 10 terabytes of sequence data under management at the end of FY 2009 and a growth rate of about 1 terabyte per month. NIH's Influenza Virus Resource database, comprising information obtained from the NIH Influenza Genome Sequencing Project and GenBank, contains more than 90,000 influenza virus sequences, including the sequences of more than 2,000 whole influenza genomes. In spring 2009, with the rapid emergence of the 2009 H1N1 pandemic, the database received more than 2,200 influenza sequences from the Centers for Disease Control and Prevention and laboratories from 35 countries. This resource enables scientists to compare influenza virus strains so that emergent variants can be identified more rapidly and vaccines developed accordingly. As the library of viral sequences grows, it will be an increasingly important reference to help further understand how avian viruses spread to humans, and how influenza activity spreads throughout the world.

Considerable effort has been aimed at supporting the analysis of data from GWAS, which explore the connection between specific genes (genotype information) and observable diseases or conditions (phenotype information, such as diabetes, high blood pressure, or obesity). NIH's dbGaP (database of Genotype and Phenotype) houses data from a number of GWAS, including those funded by NIH. By the end of 2009, dbGaP included results from more than 40 GWAS, including genetic analyses related to such diseases as Parkinson's disease, amyotrophic lateral sclerosis, diabetes, alcoholism, lung cancer, and Alzheimer's disease. NIH's GWAS policy, which went into effect in January 2008, encourages NIH grantees to submit their GWAS data to dbGaP and establishes procedures for making it available to other researchers to speed up disease gene discovery while at the same time protecting the privacy of research subjects in genomics studies.

By the end of 2009, dbGaP (database of Genotype and Phenotype) included results from more than 40 genome-wide association studies, including genetic analyses related to such diseases as Parkinson's disease, amyotrophic lateral sclerosis, diabetes, alcoholism, lung cancer, and Alzheimer's disease.

In addition, several NIH ICs have established genetics repositories to accelerate research and multidisciplinary collaborations in specific disease areas. Programs such as the NEI eyeGENE, NIMH Genetics Repository, the NINDS Human Genetics Repository, the NIEHS Chemical Effects in Biological Systems (CEBS) Knowledge Base, and the NIA Genetics of Alzheimer's Disease Data Storage Site give researchers access to vast storehouses of genetic and genomic data, DNA samples, and clinical data, along with informatics tools designed to facilitate their analyses. The wide availability of information linking genotype to phenotype should help researchers better understand gene-based diseases and speed development of effective therapies.

Other NIH-supported genetic databases contain information on model organisms, which are widely used by researchers to understand disease processes and develop new therapeutic strategies and tools that can be transferred to humans. The NIH-funded Rat Genome Database, for example, combines information on the genome, genes, and disease traits of different strains of rats with related information on the mouse and human genomes. WormBase is an international consortium of biologists and computer scientists dedicated to providing the research community with accurate, current, accessible information concerning the genetics, genomics, and biology of *C. elegans* and related organisms. The Universal Protein Resource (UniProt) Knowledgebase offers the scientific community free access to a comprehensive source of information on protein sequences and related functional information.

Disease Registries and Surveillance Systems: Tracking and Monitoring Disease

Disease registries collect information about the occurrence of specific diseases, such as cancer and Parkinson's disease, the kinds of treatment that patients receive, and other information that might be relevant to researchers or public health officials. Increasingly, disease registries also include genomic data from registered patients. Registry information can therefore help identify causal factors of disease, assess the effectiveness of various interventions, and identify questions of concern to researchers, clinical professionals, and policymakers.

Disease Registries, Databases, and Biomedical Information Systems

NIH-supported disease registries have paid many dividends over the years. Recently, for example, with the participation of patients from the Alopecia Areata Registry, NIH-supported scientists discovered four chromosomal locations that appear to be associated with susceptibility to this common autoimmune disease, which is characterized by patchy hair loss. Understanding the mechanisms of the genes found at these locations could lead to the development of an effective treatment for the disease, which is presently untreatable.

Disease registries have been employed for research on other autoimmune disorders, including Sjogren's Syndrome, one of the most prevalent. A significant roadblock for moving discoveries ahead in the field of Sjogren's Syndrome is a lack of data and biospecimens available for research. Recognizing the problem, NIH spearheaded an effort to establish patient registries at two extramural institutions, as well as through its own intramural program. These groups work together to generate and share genome-wide genotyping data and clinical information from the cohorts enrolled through these efforts with the general research community. Similarly, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) aims to establish centers in multiple regions of the world for the collection and harmonization of data that can be used by an international research consortium to address unique and evolving research questions in HIV/AIDS that are currently unanswerable by single cohorts. High-quality data are being collected by researchers throughout the world. This initiative provides a means to establish and implement methodology to effectively pool the collected data—thus providing a cost-effective means of generating large datasets to address high-priority research questions.

The inclusion of genomic information in disease registries makes them valuable resources for investigating the contribution of genes and genetic variation to diseases of interest. To spur such research, NIH collaborated with the University of North Carolina's General Clinical Research Center to launch a large volunteer DNA banking project named the Environmental Polymorphisms Registry (EPR), which will collect DNA samples from up to 20,000 individuals in the greater North Carolina Triangle Region. These samples will be available to scientists to look for genes that may be linked to common diseases such as diabetes, heart disease, cancer, asthma, and many others. In addition, NIH supports the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). The goal of GenTAC is to establish a registry of patients with genetic conditions that may be related to thoracic aortic aneurysms—a disorder that weakens the main artery from the heart—and to collect medical data and biologic samples. The samples and data are made available to qualified investigators to enable research on effective medical practices and to advance the clinical management of genetic thoracic aortic aneurysms, and other cardiovascular complications. NIH supports several other registries associated with specific diseases, including lupus, muscular dystrophy, and rheumatoid arthritis.

The International Epidemiologic Databases to Evaluate AIDS aims to establish centers in multiple regions of the world for the collection and harmonization of data that can be used by an international research consortium to address unique and evolving research questions in HIV/AIDS that are currently unanswerable by single cohorts.

Registries also serve as an effective mechanism to gather data on the incidence, prevalence, and natural history of diseases. The NIH-supported California Parkinson's Disease Registry, for example, enables researchers to identify the possible environmental and genetic origins of this progressive neurological disorder suffered by an estimated 1.5 million Americans. Data in the registry can help to determine whether race, ethnicity, gender, age, environmental factors, or place of residence influence the likelihood of getting the disease, and can help track incidence and demographic trends.

Registries also provide a valuable source of information for tracking the effectiveness of particular treatments or interventions. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), for example, is a national registry for patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure. The registry is supported jointly by NIH, the Food and Drug Administration, and the Centers for Medicare and Medicaid Services. Use of standardized terminologies helps ensure that the data collected will facilitate improved patient

evaluation and management while aiding in better device development. INTERMACS also is expected to facilitate appropriate regulation and reimbursement of the implantation of mechanical circulatory support devices.

Registries also are integral elements of more comprehensive NIH programs designed to monitor and analyze disease trends in the United States. For example, the SEER program has a 35-year track record of identifying emerging trends, geographic variation, ethnic disparities, and other patterns that have provided new directions for epidemiologic research into the cause, progression, and control of cancer. SEER collects and publishes cancer incidence and survival data from cancer registries covering approximately 26 percent of the American population. De-identified data is made available for research, and an interactive query system is available on its website. SEER data provided critical insight into the relationship between hormone therapy and breast cancer incident rates. SEER data recently have been enhanced by linking persons in SEER to Medicare enrollment and utilization data. The SEER-Medicare data are longitudinal and can be used to assess health care received prior to a cancer diagnosis, at the time of diagnosis, and after initial treatment until death. There have been more than 400 peer-reviewed publications resulting from SEER-Medicare data, adding to the thousands of publications based on SEER.

Surveillance and monitoring programs also are crucial sources of information and analysis for policymakers, legislators, public health officials, clinicians, and the public. SEER participates in Cancer Control P.L.A.N.E.T., a Web portal that provides links to comprehensive cancer control resources and data for public health professionals. NIH supports several epidemiologic programs designed to gather ongoing data and monitor emerging drug abuse trends in adolescents and other populations, helping to guide national and global prevention efforts, drug control, and public health policy. Among the projects are the Monitoring the Future (MTF) Survey, which has been tracking trends in substance use, attitudes, and beliefs among adolescents and young adults in the United States since 1975, and the Community Epidemiology Work Group (CEWG), which provides ongoing community-level surveillance of drug abuse through analysis of quantitative and qualitative research data. CEWG findings reported in 2008 and 2009 show decreases in methamphetamine indicators (e.g., treatment admissions), suggesting that the problems that had escalated in the first half of the decade may have stabilized or declined.

NIH supports several epidemiologic programs designed to gather ongoing data and monitor emerging drug abuse trends in adolescents and other populations, helping to guide national and global prevention efforts, drug control, and public health policy.

NIH also supports the Alcohol Policy Information System (APIS), an online database that provides detailed information on a wide variety of alcohol-related policies in the United States at both State and Federal levels. Designed primarily as a tool to encourage and facilitate research on the effects and effectiveness of alcohol-related public policies in the United States, APIS simplifies the process of ascertaining the state of the law for studies on the effects and effectiveness of alcohol-related policies.

Standardized Vocabularies, Data Protocols, and Tools

NIH continues to invest in tools that can increase the utility of its scientific databases and medical information sources. A key component of such efforts relates to the development and maintenance of standards and vocabularies for use in information systems used for research and clinical care, including electronic health records. Medical terminology can be difficult to remember and can vary from one laboratory or clinical facility to another. Often there are many names for a single concept (e.g., cancer of the colon, colonic neoplasm, colon cancer). Standard vocabularies and ontologies (models of the relationships between concepts) improve information search, retrieval, and exchange by endowing systems with the ability to automatically perceive and retrieve information about related terms. As expansion of scientific frontiers produces new concepts, terms, and relationships, standard vocabularies must be regularly revised so that articles and other data can be properly indexed and search engines can find relevant and related terms.

Disease Registries, Databases, and Biomedical Information Systems

NIH continues to update the Unified Medical Language System (UMLS), which is used heavily in advanced biomedical research and data mining worldwide. The UMLS Metathesaurus, with more than 7.7 million concept names from more than 100 vocabularies, is a distribution mechanism for standard code sets and vocabularies used in health data systems. Many institutions apply UMLS resources in a wide variety of applications including information retrieval, natural language processing, creation of patient and research data, and the development of enterprise-wide vocabulary services for electronic health records.

NIH is pursuing research and development on robust and scalable approaches to synthesizing, representing, updating, and deploying electronic knowledge and decision algorithms for use in conjunction with electronic health records.

The broad deployment and use of advanced electronic health records will provide expanded opportunities for access to biomedical knowledge and advanced decision support for the public, their health care providers, and the public health workforce. To turn this potential into effective reality, NIH is pursuing research and development on robust and scalable approaches to synthesizing, representing, updating, and deploying electronic knowledge and decision algorithms for use in conjunction with electronic health records. NLM serves as the central coordinating body for clinical terminology standards across the HHS and works closely with the Office of the National Coordinator for Health Information Technology (ONC) to support nationwide implementation of an interoperable health information technology infrastructure. NIH develops and licenses key clinical terminologies that are designated as standards for health information exchange in the United States. It produces RxNorm, a standard clinical drug vocabulary, supports the Logical Observation Identifiers Names and Codes (LOINC) nomenclature for laboratory tests and patient observations, and collaborates with the International Health Terminology Standards Development Organisation to promote international adoption of the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT). In FY 2009, NIH released the first version of the CORE Problem List Subset of SNOMED CT, designed to facilitate coding of problem list data in electronic health records by mapping frequently used terms from seven large-scale health care institutions to corresponding SNOMED CT concepts. (The problem list is often the first part of the clinical narrative in an electronic health record that is codified with some controlled vocabulary.) The Newborn Screening Codes and Terminology Guide, a Web portal to support more effective use of newborn screening laboratory test information, was created in FY 2009 in collaboration with the ONC, the Health Resources and Services Administration, and newborn screening organizations.

Common terminologies are a key enabler of related research and development to exploit the inherent relationships among information in disparate databases and support the interlinking of data systems. PubChem's chemical structure and bioassay records, for example, are interlinked with the biomedical literature in PubMed and with three-dimensional protein structure records. This integration provides many routes by which biomedical researchers may discover the candidate probes developed by the Molecular Libraries Initiative. A researcher examining a protein sequence record, for example, may see that a particular protein has been screened, view the active compounds, and examine structure-activity relationships using PubChem analysis tools. Another NIH resource, the Daily Med, is an official distribution mechanism for FDA-approved packaging information (drug label inserts) that links to other sources of drug information, including MedlinePlus, ClinicalTrials.gov, and PubMed. More than 60,000 people subscribe to its RSS data feeds.

NIH's Discovery Initiative, launched in FY 2006-2007 and continuing into FY 2008-2009 aims to take database linking to the next level. The Discovery Initiative will improve the presentation of results from search queries conducted across a range of NIH databases so that users, who often do not go beyond retrieving the basic results of a search query, are more likely to be drawn to related information that could lead to serendipitous discoveries, even if that information resides in another NIH database. NIH's Collective Intelligence Initiative aims to facilitate data re-use and knowledge discovery by using controlled vocabularies and ontologies to pull together and analyze related information from databases across the ICs.

Large-Scale Informatics Infrastructure

NIH also has embarked on a number of large-scale initiatives to develop and deploy infrastructure and tools for storing, sharing, integrating, and analyzing the large volumes of data routinely generated in research laboratories and in clinical settings. These initiatives tend to produce not only storehouses for data generated by research, but also larger scale networks for sharing data, linking researchers, and conducting further research. NIH supports a number of clinical research networks, for example, infrastructure that allows standardized data reporting and sharing of information across clinical studies. (Also see the section on *Clinical and Translational Research* in Chapter 3.)

In the area of cancer research, NIH has established the Cancer Biomedical Informatics Grid® (caBIG®), a collaborative information network for all of NCI's advanced technology and program initiatives that aims to enable collaborative research and personalized, evidence-based care. The network connects scientists, practitioners, and patients, enabling the collection, analysis, and sharing of data and knowledge along the entire research pathway from bench to bedside. Specific biomedical research tools under development by caBIG® include clinical trial management systems, tissue repositories and pathology tools, imaging tools, and a rich collection of integrative cancer research applications. Ongoing collaborations with research and bioinformation organizations in China, India, and the United Kingdom are driving international adoption of caBIG® resources. The caBIG® infrastructure also supports a new health care ecosystem, BIG Health, launched in 2008 in collaboration with various stakeholders in biomedicine (e.g., government, academia, industry, nonprofits, and consumers) in a novel organizational framework to demonstrate the feasibility and benefits of personalized medicine. BIG Health will provide the foundation for a new approach in which clinical care, clinical research, and scientific discovery are linked.

Other efforts aim to provide the informatics infrastructure to advance basic research and clinical studies across the spectrum of biomedical sciences. NIH's Biomedical Informatics Research Network (BIRN) is a virtual community of shared informatics resources. BIRN's grid computing technology makes digital research data freely available for sharing and exchange among communities of researchers; its data integration tools allow searching across distributed databases; and it provides tools for data analysis, management, and collaborative research. (Also see the section on *Technology Development* in Chapter 3.) The CardioVascular Research Grid (CVRG) provides infrastructure for sharing cardiovascular data and data analysis tools. The CVRG builds on and extends tools developed in the caBIG® and BIRN projects to support national and international collaborations in cardiovascular science.

A Disaster Information Management Research Center was established in FY 2008 to facilitate access to disaster information, promote more effective use of libraries and disaster information specialists in disaster management efforts, and ensure uninterrupted access to critical health information resources when disasters occur.

The Neuroscience Information Framework (NIF), part of NIH's Neuroscience Blueprint, aims to advance neuroscience research by enabling discovery and access to research data and tools worldwide through an open source, networked environment. By the end of FY 2009, more than 2,300 Web-accessible information resources were listed in the NIF registry. NIF also supports the NeuroLex project, which aims to define neurological terms and their relationships to simplify information retrieval and sharing. NeuroLex consisted of approximately 17,000 neuroscience concepts at the end of FY 2009. A related effort, the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC), facilitates finding and comparing structural and functional neuroimaging tools and resources. Collecting and pointing to standardized information about tools, this site helps researchers find the right structural or functional neuroimaging tool or resource and determine whether it can contribute to a given research endeavor. More than half the tools available through the Clearinghouse previously were unavailable for sharing. Since its release at the beginning of FY 2008, more than 50,000 software files have been downloaded from its award-winning website.

The Bioinformatics and Computational Biology initiatives of the NIH Roadmap continue to make progress toward creation of a national biomedical data and information management system. Through the system, biologists, chemists,

Disease Registries, Databases, and Biomedical Information Systems

physicists, computer scientists, and physicians anywhere in the country will be able to use a common set of software tools to analyze, integrate, model, simulate, and share data. The National Centers for Biomedical Computing are a central focus of this effort, providing funding for seven centers that cover systems biology, image processing, biophysical modeling, biomedical ontologies, information integration, and tools for gene-phenotype and disease analysis. The Centers collaborate with other NIH-funded institutions on topics ranging from biomechanics to standards development for data mining, and cross-Center working groups pursue activities of common interest, such as Biositemaps, which assist users in locating, querying, composing or combining, and mining biomedical information from databases that are distributed across the Centers.

NIH also develops advanced information infrastructure to assist emergency responders when disaster strikes. A Disaster Information Management Research Center was established in FY 2008 with the aim to facilitate access to disaster information, promote more effective use of libraries and disaster information specialists in disaster management efforts, and ensure uninterrupted access to critical health information resources when disasters occur. A disaster information website provides access to a broad range of emergency preparedness and response information. The Center also collaborates with the Navy National Medical Center, Suburban Hospital, Johns Hopkins Medicine, and the NIH Clinical Center through the Bethesda Hospital Emergency Preparedness Partnership. The Partnership provides backup communication systems and develops tools for patient tracking, information sharing and access, and responder training, serving as a model for hospitals across the Nation.

Biomedical Informatics Research and Training

Ensuring continued advances in biomedical informatics resources requires active support of fundamental research that seeds the further development of new tools, resources, and approaches. It also is critical to generate a continuous supply of skilled biomedical informatics researchers, information specialists (such as medical librarians), and life sciences researchers trained in bioinformatics. NIH continues to expand its efforts in bioinformatics research and training in response to the growing importance of informatics in the biomedical and life sciences.

NIH supports research in new technologies to address issues such as: interoperability of data systems, compatibility of computer software across medical institutions, security of data during transmission, compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), availability of affordable data systems for patient care providers, and integration of medical decision support information in medical data systems. Several ICs fund informatics research projects within their areas of specialization. NLM remains the primary Federal sponsor of biomedical informatics research, and its extramural grants program supports research on the characterization, management, and efficient use of data, information, and knowledge in health care and basic biomedical sciences. Grants funded in FY 2008-2009 explored informatics challenges related to clinical care, biomedical research, genomics, and public health. NLM's most recent long-range plan, *Charting a Course for the 21st Century*, identifies a number of emerging informatics challenges that will demand continued research and development.

Funds from the American Reinvestment and Recovery Act will allow NIH to support an additional 56 2-year slots at 10 of its training programs for 2009 and 2010.

NIH also is the principal source of support for research training in biomedical informatics, providing research training grants to 18 institutions that enrolled 270 trainees in FY 2009. ARRA funds will allow NIH to support an additional 56 2-year slots at 10 of its training programs for 2009 and 2010. NIH also implemented a Diversity Short-Term Trainee Program in FY 2008 that supported 18 trainees in 7 training programs and sponsors an Informatics Training for Global Health Program, which supports informatics research training in low- and middle-income country institutions in partnership with U.S. institutions and investigators. Training is integrated with ongoing research at the foreign institutions to develop informatics capacity and support research. Training must address the health and informatics needs of the collaborating countries. (Also see the section on *Research Training and Career Development* in Chapter 3.)

Conclusion

The results of NIH's commitment to disease registries, databases, and biomedical information systems are apparent in the following highlights describing some of the important accomplishments and ongoing initiatives.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research

I = Supported through **I**ntramural research

O = **O**ther (e.g., policy, planning, or communication)

COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program

GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct

ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

NIH Scientific Databases: Enhancing Access to Research Information

PubMed®/MEDLINE®: NIH continued to expand PubMed/MEDLINE as a tool for biomedical research, clinical medicine, and consumer health. Nearly 1.4 million articles from the biomedical journal literature were added to PubMed/MEDLINE in FYs 2008-2009. The Indexing 2015 initiative continues to pursue increases in the speed and efficiency of indexing through natural language processing and other automated techniques, and in FYs 2008-2009, the GPRA goal of reducing the time to catalog new journals added to NLM's collection was achieved. Drawing on results of the NCBI Discovery Initiative, enhancements were made to PubMed search capabilities to expand the number and highlight the visibility of links to related information across multiple databases.

- For more information, see <http://pubmed.gov>
- (I) (NLM) (GPRA)

PubMed Central (PMC): NIH made significant enhancements to PMC, an online repository of full-text biomedical journal articles. Since February 2007, PMC has doubled the number of articles to 1.9 million in September 2009. Usage also has risen by 60 percent to more than 360,000 users per day. A part of the growth has stemmed from the NIH Public Access policy changing from a voluntary to a mandatory program in April 2008. Under the Public Access policy, all NIH-funded research articles must be deposited in PMC. The NIH Manuscript Submission system streamlines the process for NIH-funded authors submitting their manuscripts to PMC, and more than 5,000 manuscripts a month are received, compared to less than 1,000 under the previous voluntary Public Access policy in 2007. Through PMC agreements with publishers, a growing number of journals, now more than 700, offer full text of their contents to PMC either immediately upon publication or within 12 months. To foster international cooperation on preservation and access to biomedical literature, NIH made PMC software available to archiving organizations outside the United States and worked with the Wellcome Trust and other major United Kingdom (UK) research funders to establish a collaborating PMC site in the UK, which has been operational since 2008. In 2009, NIH partnered with the Canadian Institutes of Health Research and the National Research Council's Canada Institute for Scientific and Technical Information to establish PMC Canada.

- For more information, see <http://www.pubmedcentral.nih.gov>
- For more information, see <http://ukpmc.ac.uk>
- (I) (NLM)

Disease Registries, Databases, and Biomedical Information Systems

PubChem: PubChem is an open repository for data on the properties of small molecules, including bioactivity test results. It began in 2004 as part of NIH's Molecular Libraries Program, which aims to discover new chemical probes through high-throughput biological screening. As of FY 2009, there were more than 25 million unique structures and 1,700 bioassays. These assays contain information on the biological activities of 700,000 compounds, yielding more than 50 million bioactivity results, and have been contributed by 34 academic, government, and commercial organizations. Through the PubChem website, more than 50,000 scientists a day rapidly search chemical structures, retrieve and compare screening results, explore structure-activity relationships, and identify potential molecular targets.

- Wang Y, et al. *Nucleic Acids Res* 2009;37(Web Server issue):W623-33. PMID: 19498078. PMID: PMC2703903.
- For more information, see <http://pubchem.ncbi.nlm.nih.gov/>
- (I) (NLM)

TOXicology Data NETWORK (TOXNET): TOXNET is a cluster of 13 databases covering toxicology, hazardous chemicals, environmental health, and related topics. It is a primary reference for toxicologists, poison control centers, public health administrators, physicians, and other environmental health professionals, and includes databases such as Hazardous Substances Data Bank, TOXLINE, GENE-TOX, and the Toxic Release Inventory. In FY 2008, the Carcinogenic Potency Database at the University of California, Berkeley, which reports analyses of animal cancer tests and is in support of cancer risk assessments, was added to the databases searchable through the TOXNET search engine. TOXNET is highly used, with nearly 600,000 users in FYs 2008 and 2009. Enhancements based on user feedback were made in FY 2008.

- (I) (NLM)

National Database for Autism Research: The National Database for Autism Research (NDAR) is a collaborative biomedical informatics system created by NIH to provide a national resource to support and accelerate research in autism spectrum disorder (ASD). NDAR hosts human genetic, imaging, and phenotypic research data relevant to ASD, making these data available to qualified researchers. NDAR also has the capability to allow investigators to use NDAR for data sharing among select collaborators in ongoing studies. Through its Data Dictionary, NDAR will foster the development of a shared, common understanding of the complex data landscape that characterizes ASD research. Finally, its architecture facilitates linkage of NDAR with other significant data resources, regardless of their location or ownership and in ways that respect the policies and implementations of those other data resources.

- For more information, see <http://ndar.nih.gov/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E/I) (NIMH, CIT, NICHD, NIDCD, NIEHS, NINDS)

National NeuroAIDS Tissue Consortium: The National NeuroAIDS Tissue Consortium (NNTC) is a repository of brain tissue and fluids from highly characterized HIV-positive individuals. Established as a resource for the research community, the NNTC includes information from more than 2,280 participants in its clinical evaluation/tissue donation program, including nearly 750 brains, thousands of plasma and cerebrospinal fluid samples, and additional organs and nerves of interest.

- For more information, see <http://www.hivbrainbanks.org/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NIMH, NINDS)

ClinicalTrials.gov: ClinicalTrials.gov was significantly modified during FY 2008-2009 to respond to new clinical trial registration and results reporting requirements established by the FDA Amendments Act of 2007 (PL 110-85). The existing registry was expanded to accommodate the submission of more information about a larger number of trials, including those trials of FDA-regulated drugs, biological products and devices that now are required to register. In addition, NIH developed and implemented results modules to accept and display to the public summary results information, including adverse event information from registered trials. Mandatory reporting of results began in September 2008, with mandatory submission of adverse event information following in September 2009. During FYs 2008-2009, more than 34,000 trials were newly registered with ClinicalTrials.gov, raising the total number of registered trials to 80,000. In addition, summary results of more than 830 clinical trials were submitted and made available at ClinicalTrials.gov, with the rate of results submission approaching 200 trials per month by the end of FY 2009. To solicit input on issues to be considered in rulemaking for further expansion of ClinicalTrials.gov, a public meeting was held in April 2009; more than 200 participants attended the meeting, and more than 70 written comments were submitted to a public docket.

- This example also appears in Chapter 3: *Clinical and Translational Research*
- (I) (NLM)

The Biomedical Translational Research Information System: The NIH intramural program uses a wide variety of clinical and research data management systems to gather clinical research data. The single largest system is the Clinical Research Information System (CRIS) at the NIH CC; however, many of the other 26 ICs at NIH have their own systems, as do many laboratories at the ICs and even individual researchers within the laboratories. Thus, research data for individual clinical trials and on individual subjects are scattered across multiple diverse systems. The Biomedical Translational Research Information System (BTRIS) project, initiated in 2008 and made available in 2009, includes a sophisticated data warehouse that currently contains the data on more than 447,000 subjects from 8,800 protocols, gathered from the CRIS system (2004 to present), archived data from CRIS' predecessor system (1976 to 2004), and data from systems at NIAID and NIAAA. BTRIS provides NIH researchers with a user-friendly reporting application to obtain data on subjects in their own protocols from across all these sources. They also are able to perform queries against all data on all research subjects from all clinical trials (in de-identified form), to allow them to ask new questions of the data, look for previously unrecognized correlations, and gain new insights through the reuse of data that NIH has been collecting for the past three decades.

- For more information, see <http://btrिस.nih.gov>
- (I) (CC)

ProtoType: ProtoType is an assisted protocol authoring tool that provides a systematic framework where protocols can be developed and maintained throughout their life cycle. ProtoType includes fully customized documents tailored toward individual Institutional Review Boards (IRBs), taking all the guesswork out of creating a protocol and allowing the investigator to focus on authoring. By capturing the entire authoring process electronically, the protocol can be moved easily between the IC IRB, NIH CC, and other Institutes and investigators while tracking the state of the protocol. Ultimately, ProtoType will be an online archive of all protocols submitted by each principal investigator and will maintain the protocols' histories. ProtoType currently has incorporated templates from 4 of the 12 NIH IRBs, with more than 200 distinct investigators using the system.

- For more information, see <https://prototype.cc.nih.gov>
- (I) (CC)

Disease Registries, Databases, and Biomedical Information Systems

Genomic Information Systems: Understanding the Genetic Basis of Disease

Influenza Virus Resources: NIH maintains the Influenza Virus Resource, a database of influenza virus sequences that enables researchers around the world to compare different virus strains, identify genetic factors that determine the virulence of virus strains, and look for new therapeutic, diagnostic, and vaccine targets. The resource was developed using publicly accessible data from laboratories worldwide in addition to targeted sequencing programs such as NIH's Influenza Genome Sequencing Project. Updated daily, this comprehensive sequence resource includes more than 90,000 influenza sequences and more than 2,000 complete genomes. In the spring of 2009, with the rapid emergence of the 2009 H1N1 pandemic, the database received more than 2,200 influenza sequences from publicly accessible databases and included sequences from CDC and labs from 35 countries. By the end of 2009, nearly 10,000 H1N1 sequences were in the database. The combination of extensive sequence data and advanced analytic tools provided researchers worldwide immediate access for investigating the rapid spread of this flu and developing vaccines for combating it. Other influenza virus information resources also were developed in response to 2009 H1N1. To facilitate access to the scientific literature, a pre-formulated search for 2009 H1N1 papers was added to PubMed. A 2009 H1N1 Flu page with comprehensive information on Federal response, international resources, transmission, prevention, treatment, genetic makeup, and veterinary resources was added to Enviro-Health Links, which provides links to toxicology and environmental health topics of recent special interest, including information in Spanish. For the general public, patients, family members, and caregivers, a health topic on 2009 H1N1 flu, in Spanish and English, was added to the MedlinePlus consumer health resource.

- Bao Y, et al. *J Virol* 2008;82(2):596-601. PMID: 17942553. PMCID: PMC2224563.
- For more information, see <http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html>
- For more information, see <http://www.pubmed.gov>
- For more information, see <http://sis.nlm.nih.gov/enviro/swineflu.html>
- For more information, see <http://www.nlm.nih.gov/medlineplus/h1n1fluswineflu.html>
- For more information, see <http://www.nlm.nih.gov/medlineplus/spanish/h1n1fluswineflu.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Molecular Biology and Basic Research*
- (I) (NLM)

Genome-Wide Association Studies: With unprecedented speed, researchers have used an approach called genome-wide association studies (GWAS) to explore genetic variants and their complex relationships to human health and disease. GWAS research has linked a stunning number of genetic variants to common conditions—more than 130 in 2008 alone. For example, the obesity epidemic and its related health conditions pose a great challenge for the Nation. In 2008, the Genetic Investigation of Anthropometric Traits consortium identified six genes associated with body mass index, a key indicator for obesity. Also in 2008, three GWAS of lung cancer implicated several genes already known to be linked to nicotine addiction. In a feat that would not have been possible without the power of whole genome analysis, the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium in 2009 gathered data from participants in long-running studies to reveal genetic variants associated with an increased risk of stroke. Identification of genetic variants associated with common diseases opens new windows into the biology of health and disease. This work also raises the possibility of someday using genetic testing, in combination with family history, to identify at-risk, pre-symptomatic individuals who might benefit from personalized screening and preventive therapies.

- For more information, see <http://www.genome.gov/27528559>
- For more information, see <http://www.genome.gov/27529231>
- For more information, see <http://www.genome.gov/27531390>
- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
- (E, I) (NHGRI, NIDDK, NCI, NIA, NHLBI, NIMH, NINDS)

Database of Genotype and Phenotype (dbGaP): Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics, and other scientific data, NIH established dbGaP to house the results of genome-wide association studies (GWAS), which examine genetic data of de-identified subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2009, dbGaP included results from more than 40 GWAS, including genetic analyses related to such diseases as Parkinson's disease, ALS, diabetes, alcoholism, lung cancer, and Alzheimer's disease. dbGaP is the central repository for many NIH-funded GWAS to provide for rapid and widespread distribution of such data to researchers and accelerate the understanding of how genes affect the susceptibility to and severity of disease.

- For more information, see <http://view.ncbi.nlm.nih.gov/dbgap>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*
- (I) (NLM)

Genome-Wide Association Studies of Autoimmune Disease Risk: In recent years, genome-wide association studies (GWAS) have transformed the identification of gene regions related to disease risk, through an unbiased analysis of patients with a disease, in comparison with people who don't have it. These GWAS require large numbers of patients and individuals without the disease to obtain statistically significant results. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects, in addition to productive, multisite collaborations across the United States, including international researchers and contributions from the NIH Intramural Research Program. GWAS have yielded important information about disease risk, as well as understanding of disease pathways and potential therapeutic targets, in several autoimmune diseases in the past 2 years. Diseases studied include psoriasis, rheumatoid arthritis, systemic lupus erythematosus (or lupus), ankylosing spondylitis, and type 1 diabetes. Initial results from GWAS require confirmation by replication in additional groups of patients. More detailed localization of disease risk genes can be achieved through comprehensive DNA sequencing of candidate gene regions. New NIH initiatives are supporting these follow-up studies, which are critical to validating GWAS findings.

- Plenge RM, et al. *Nat Genet* 2007;39(12):1477-82. PMID: 17982456. PMCID: PMC2652744.
- Wellcome Trust Case Control Consortium, et al. *Nat Genet* 2007;39(11):1329-37. PMID: 17952073. PMCID: PMC2680141.
- Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
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- Nair RP, et al. *Nat Genet* 2009;41(2):199-204. PMID: 19169254. PMCID: PMC2745122.
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- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/10_04.asp
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-09-135.html>
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2008/Anky1_Spond_gene.asp
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-08-123.html>
- For more information, see <http://www.nature.com/ng/journal/v41/n6/abs/ng.381.html>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Genomics*
- (E/I) (NIAMS, NCRR, NHGRI, NHLBI, NIAID, NICHD, NIDA, NIDCR, NIDDK)

The National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE): Over the past 20 years, vision researchers have been remarkably successful in identifying the genetic basis of eye disease. More than 400 disease genes causing a wide range of eye diseases have been isolated, revealing unimagined complexity. Although some gene mutations lead to clearly defined clinical characteristics, or phenotypes, many other mutations are clinically indistinguishable from one another. Matching genetic testing with the disease phenotype will help to resolve this complexity and allow clinicians

Disease Registries, Databases, and Biomedical Information Systems

to diagnose specific diseases more accurately. However, commercial testing for rare eye diseases is limited. eyeGENE will expand the Nation's capacity to genotype patients with eye disease, thus improving patients' knowledge of their condition and the potential to personalize treatment eventually. From a research standpoint, patient DNA samples are invaluable for molecular studies, and patient registries are critical for patient recruitment for clinical trials. To address these needs, the NIH created eyeGENE, a partnership between government, health care providers, private industry, and scientists to broaden research resources and increase patient accessibility to diagnostic genetic testing. eyeGENE will provide researchers with patient genotype and phenotype data to elucidate ophthalmic disease genes and genetic modifiers, and enhance future enrollment of subjects in clinical trials.

- Brooks BP, et al. *Arch Ophthalmol* 2008;126(3)424-5. PMID: 18332328.
- For more information, see <http://www.nei.nih.gov/resources/eyegene.asp>
- (E/I) (NEI)

NINDS Human Genetics Repository: In 2002, NINDS established the Human Genetics Repository to collect, store, characterize, and distribute DNA samples and cell lines and standardized clinical data for the research community. By June 2009, the repository held material from 27,166 subjects, including those with cerebrovascular disease (8,625), epilepsy (1,356), Parkinson's disease (5,700), motor neuron diseases such as amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, (2,631), and Tourette Syndrome (1,185), as well as control samples (6,162). The ethnically diverse collection represents populations from the United States and several other countries. Investigators have submitted or published more than 100 scientific articles based on data from this resource, and technological advances allowing whole genome screening for disease genes also have enhanced its value.

- For more information, see <http://ccr.coriell.org/Sections/Collections/NINDS/?SsId=10>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E, I) (NINDS)

Dietary Supplement Ingredient Database (DSID): Working with the Nutrient Data Laboratory, Beltsville Human Nutrition Research Center, which is part of the USDA Agricultural Research Service, and other Federal agencies, NIH developed the DSID to estimate levels of ingredients in dietary supplement products. The main features of the database include data files, a research summary, and an adult multivitamin/minerals calculator. Since more than half of American adults report taking a dietary supplement, the estimates in the DISD will improve assessment of total nutrient intake from foods and supplements.

- For more information, see <http://dietarysupplementdatabase.usda.nih.gov>
- (E) (ODP/ODS)

Dietary Supplement Labels Database (DSLID): NIH is developing a comprehensive information resource on dietary supplement labels. The current database includes information from the labels of approximately 4,000 dietary supplement products in the marketplace, including vitamins, minerals, herbs or other botanicals, amino acids, and other specialty supplements. Ingredients of dietary supplements in this database are linked to other NIH databases such as MedlinePlus® to allow users to investigate the dietary ingredients and view biomedical literature pertaining to them. NIH is piloting the development of a full-scale application that includes label information on virtually all dietary supplements sold in the United States. The future DSLID will provide comprehensive label information in a format that is user-friendly for both consumers and researchers. The information included in the database will be determined by Federal and stakeholder user groups.

- For more information, see <http://dietarysupplements.nlm.nih.gov>
- (E) (NLM, ODP/ODS)

Disease Registries and Surveillance Systems: Tracking and Monitoring Disease

Seeking Solutions for People with Sjogren's Syndrome: Sjogren's syndrome is one of the most prevalent autoimmune disorders, affecting as many as 4 million people in the United States. Nine out of 10 patients affected are female. It is an autoimmune disease that progressively destroys salivary and lachrymal glands. The most common symptoms include dry eyes, dry mouth, fatigue, and musculoskeletal pain. A significant roadblock for moving discoveries ahead in the field of Sjogren's syndrome is the lack of data and biospecimens available for research. Recognizing the problem, NIH spearheaded an effort to establish Sjogren's patient registries at two extramural institutions as well as through its own intramural program. These groups are working together to generate and share with the general research community the genome-wide genotyping data and clinical information from the cohorts enrolled through these efforts. This resource should jumpstart efforts to understand genetic contributions to Sjogren's syndrome and the etiologic overlap with related autoimmune conditions such as lupus and rheumatoid arthritis. In addition to participating in the patient registry and genotyping efforts described above, the Sjogren's Syndrome Clinic, located in the NIH CC, collects systematic clinical and laboratory data on the Sjogren's syndrome (and salivary dysfunction) population. Gene therapy and bioengineering hold promise for the repair or even replacement of salivary glands ravaged by Sjogren's syndrome. More than 300 patient visits occur annually, and the clinic is expanding its patient recruitment to accelerate the conduct of clinical trials that might shed light on this disorder.

- Korman BD, et al. *Genes Immun* 2008;9(3):267-70. PMID: 18273036.
- Roescher N, et al. *Oral Dis* 2009;15(8):519-26. PMID: 19519622. PMCID: PMC2762015.
- Nikolov NP, Illei GG. *Curr Opin Rheumatol* 2009;21(5):465-70. PMID: 19568172. PMCID: PMC2766246.
- For more information, see <http://www.sjogrens.org/>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Genomics*
- (E/I) (NIDCR, CC, ORWH)

International Epidemiologic Databases to Evaluate AIDS (IeDEA): The goal of the IeDEA program is to conduct analyses based on comparable data from multiple regions and studies. This initiative has established international regional centers for the collection and harmonization of data and has created an international research consortium to address unique and evolving research questions in HIV/AIDS currently unanswerable by single cohorts. High-quality data are being collected by researchers throughout the world. This initiative provides a means to establish and implement methodology to pool the collected data effectively—thus providing a cost-effective means of generating large data sets to address the high-priority research questions. Combination of data collected under various protocols frequently is very difficult and not as efficient as the collection of predetermined and standardized data elements. By developing a proactive mechanism for the collection of key variables, this initiative will enhance the quality cost effectiveness and speed of HIV/AIDS research. Participating regions include Canada and the United States, the Caribbean and Central and South America, Asia and Australia (excluding China), West Africa, Central Africa, East Africa, and Southern Africa.

- For more information, see <http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIAID, NCI, NICHD)

Environmental Polymorphisms Registry: NIH, in collaboration with the University of North Carolina's General Clinical Research Center, has launched a large volunteer DNA banking project named the Environmental Polymorphisms Registry (EPR). The goal of the EPR is to collect DNA samples from 20,000 individuals in the greater Research Triangle Park region of North Carolina through local health care systems, study drives, health fairs, and other means. This area has a

Disease Registries, Databases, and Biomedical Information Systems

diverse population varying in age, ethnicity, economic and educational backgrounds, and health status. The EPR offers a valuable resource for human genomic studies, especially when compared to anonymous DNA registries. It was designed for scientists to screen for functionally significant alleles and to identify subpopulations of individuals with shared genotypes, and then correlate their genotypes with their phenotypes in a process known as "recruit-by-genotype." The value of the EPR lies in the ability to identify and then re-contact subjects with potentially significant polymorphisms for further study. A unique feature of the EPR is that two distinct populations are solicited, an apparently healthy population recruited from the general population as well as a clinic population recruited from various clinics and hospitals in the area. Individuals in the clinic population have a wide array of medical conditions, and their inclusion in the EPR increases the likelihood of identifying subjects with both the genotypes and phenotypes of interest. These aspects of the EPR give scientists more flexibility in designing follow-up studies while reducing the ascertainment bias that can occur in genetic epidemiology studies when subjects are recruited based on phenotype.

- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E/I) (NIEHS)

Surveillance, Epidemiology, and End Results (SEER): The SEER program provides essential data that support cancer research across NIH and collaborating agencies and organizations in the United States and around the world. SEER covers approximately 26 percent of the U.S. population, with information in its database on more than 5.7 million cancer cases. SEER registries routinely collect data on patient demographics, primary tumor site, morphology, extent of disease at diagnosis, and first course of treatment. All patients are followed annually for vital status and compilation of survival data. The SEER Program is the only comprehensive source of population-based data in the United States that includes stage of cancer at the time of diagnosis and survival rates by stage. It is the only population-based source of long-term incidence and survival data, having a 35-year history in most of its registries. SEER provides source data for the American Cancer Society Facts & Figures and the Annual Report to the Nation on the Status of Cancer. SEER is one of the most fundamental contributors to the cancer research infrastructure, adding more than 380,000 cases each year. The program sets national benchmarks for incidence and survival rates and is the primary source of reports on cancer death rates. The size of the database allows for analysis of rare cancers and cancer heterogeneity at both the tumor and patient level. The SEER database also includes prevalence information on the 11.4 million cancer survivors in the United States, allowing analysis by age and cancer site as well as time elapsed since diagnosis. There are more than 2,000 agreements executed annually for the public-use data and more than 3 million hits per month on the SEER Internet homepage.

- For more information, see <http://seer.cancer.gov>
- This example also appears in Chapter 2: *Cancer*
- (E) (NCI)

Cancer Control P.L.A.N.E.T: The Cancer Control P.L.A.N.E.T. (Plan, Link, Act, Network with Evidence-based Tools) Web portal was launched collaboratively in 2003 by NIH, Agency for Healthcare Research and Quality, American Cancer Society, Centers for Disease Control and Prevention, Commission on Cancer, and Substance Abuse and Mental Health Services Administration. The portal now has been expanded, in collaboration with the Surveillance Action Group of the Canadian Partnership Against Cancer, to include Cancer Control P.L.A.N.E.T. Canada. The Canadian site follows the same design as the U.S. site, while engaging Canadian cancer control practitioners and researchers in usability testing to ensure that the Canadian site meets their needs. Both the Canadian and U.S. sites provide a single point of access to high-quality tools and resources from multiple national organizations that can be used to design, implement, and evaluate evidence-based cancer control plans and programs. They guide local programs to resources that help them determine cancer risk and cancer burden in their geographic areas. They also help identify potential partners and provide online resources for interpreting research findings and recommendations and accessing products and guidelines for planning and evaluation.

- For more information, see <http://cancercontrolplanet.cancer.gov>
- This example also appears in Chapter 2: *Cancer*
- (E) (NCI)

A Look at Drug Abuse Trends: Local to International: Two major systems of data collection are helping to identify substance abuse trends locally, nationally, and internationally: Monitoring the Future Survey (MTF) and the Community Epidemiology Work Group (CEWG). Both help to surface emerging drug abuse trends among adolescents and other populations, and guide responsive national and global prevention efforts. The MTF project, begun in 1975, has many purposes, the primary one being to track trends in substance use, attitudes, and beliefs among adolescents and young adults. The survey findings also have been used by the President's Office of National Drug Control Policy to monitor progress toward national health goals. The MTF project includes both cross-sectional and longitudinal formats—the former given annually to 8th, 10th, and 12th graders to see how answers change over time, and the latter given every 2 years (until age 30), then every 5 years to follow up on a randomly selected sample from each senior class. CEWG, established in 1976, provides both national and international information about drug abuse trends through a network of researchers from different geographic areas. Regular meetings feature presentations on selected topics, as well as those offering international perspectives on drug abuse patterns and trends. CEWG findings reported in 2008 and 2009 show decreases in methamphetamine indicators (e.g., treatment admissions), suggesting that the problems that had escalated in the first half of the decade may have stabilized or declined. Development of a Latin American Epidemiology Network is underway. NIH also has provided technical consultation for the planning and establishment of an Asian multicity epidemiological network on drug abuse.

- For more information, see <http://www.monitoringthefuture.org/>
- For more information, see <http://www.drugabuse.gov/about/organization/CEWG/CEWGHome.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIDA)

Alcohol Policy Information System: Public policies that affect alcohol consumption and related behaviors can influence a range of health and social outcomes. The NIH has developed the Alcohol Policy Information System (APIS) to provide authoritative and detailed information on alcohol-related public policies in the United States at both the State and Federal levels. Intended primarily as a tool for researchers, the APIS website (<http://alcoholpolicy.niaaa.nih.gov>), posted in June 2003, features compilations and analyses of alcohol-related statutes and regulations. APIS is designed to simplify the process of ascertaining the state of the law for studies on the effects and effectiveness of alcohol-related policies. APIS currently provides information on 30 specific policy topics, including summary descriptions, maps, detailed comparison tables, and the specific dates on which provisions became or ceased to be effective. For most policy topics, APIS coverage begins as early as January 1, 1998, and extends through September 18, 2008. NIH issued program announcements for alcohol policy research that use APIS in 2007.

- Fell J, et al. *Alcohol Clin Exp Res* 2009;33(7):1208-1219.PMID: 19389192.
- Wagenaar AC, et al. *Addiction* 2009;104(2):179-90. PMID: 19149811.
- For more information, see <http://www.alcoholpolicy.niaaa.nih.gov>
- (E) (NIAAA)

Standardized Vocabularies, Data Protocols, and Tools

Health IT Standards and Electronic Health Records: NIH researchers are engaged in developing Next Generation electronic health records (EHRs) with advanced decision-support capabilities to facilitate patient-centered care, clinical research, and public health. As the central coordinating body for clinical terminology standards within HHS, NIH works

Disease Registries, Databases, and Biomedical Information Systems

closely with the Office of the National Coordinator for Health Information Technology (ONC) to support nationwide implementation of an interoperable health information technology infrastructure. NIH develops or licenses key clinical terminologies that are designated as standards for U.S. health information exchange. The Unified Medical Language System Metathesaurus, with more than 8.1 million concept names from more than 125 vocabularies, is a distribution mechanism for standard code sets and vocabularies used in health data systems. NIH also produces RxNorm, a standard clinical drug vocabulary; supports the LOINC nomenclature for laboratory tests and patient observations; and collaborates with the International Health Terminology Standards Development Organisation to promote international adoption of the SNOMED CT clinical terminology. In FY 2009, NIH released the first version of the CORE Problem List Subset of SNOMED CT, designed to facilitate coding of problem list data in EHRs by mapping frequently used terms from seven large-scale health care institutions to corresponding SNOMED CT concepts. The Newborn Screening Codes and Terminology Guide, a Web portal to support more effective use of newborn screening laboratory test information, was created in FY 2009 in collaboration with ONC, the Health Resources and Services Administration, and newborn screening organizations.

- For more information, see <http://www.nlm.nih.gov/research/umls>
- This example also appears in Chapter 3: *Technology Development*
- (I) (NLM)

Health Information Technology: Health information technology research that enables the integration of clinical data and medical image diagnostic and treatment data with the patient's medical history in a comprehensive electronic medical record will improve clinical decision-making. The ability to connect and exchange diagnostic information and medical images between health care providers, clinics, and hospitals will help provide the timely information that is needed for effective health care and will help reduce unnecessary, excessive, and duplicative procedures. A patient-centered approach to comprehensive electronic health records will allow patients access to their health information. This will enable patients to play an active role in their own wellness by enabling them to ask knowledgeable questions about treatment options. Additionally, patients also are empowered to provide this information to any and all health care providers as needed, independent of their location or where the medical data was created or stored. NIH supports research in new methods and technologies to address issues such as: interoperability of data systems, compatibility of computer software across medical institutions, security of data during transmission, HIPAA compliance, availability of affordable data systems for patient care providers, and integration of medical decision-support information in medical data systems.

- This example also appears in Chapter 3: *Technology Development*
- (E) (NIBIB, NLM)

Discovery Initiative for Entrez Databases: The Discovery Initiative aims to maximize the utility of NIH biomedical data resources by better exploiting their inter-linkages. For example, a PubChem record on a chemical structure might link to records for similar proteins, related protein structures, and relevant journal articles. Such linkages provide users with tremendous opportunities for exploration and scientific discovery, but are underutilized currently. The Discovery Initiative aims to improve the retrieval and presentation of results so that users are drawn more readily to related data that could lead to serendipitous discoveries. Improvements have been made in the search interface through the use of "sensors" that can detect certain categories of search terms automatically, such as genes or drugs, and then direct the user's attention to resources that may augment the original search. Through these linkages, users are better able to traverse the 40-plus databases in the Entrez network, ranging from topics such as human genetic disorders and genome projects to cancer chromosomes and protein structure.

- National Center for Biotechnology Information. Featured Resource: Improvements to NCBI Services Promote Discovery. *NCBI News* 2009;February:1.
- (I) (NLM)

Collective Intelligence for Knowledge Discovery: NIH has started a new NIH initiative in collective intelligence. The goal is to create deep repositories of knowledge backed by controlled vocabularies or ontologies, and to create or enhance semantically interoperable applications capable of discovering knowledge hidden within these repositories. Current applications such as the Human Salivary Proteome Annotation System, the Common Assay Reporting System, and the caBIG Protocol Lifecycle Tracking Tool are among the initial steps of a knowledge infrastructure. These applications harvest the collective knowledge of targeted scientific communities to store protocols, data, and results. Other tools developed for this initiative (e.g., the context-sensitive text mining system for identification of high-risk, high-reward research) use statistical natural language processing to discover new knowledge, such as, whether in peer review, an application for funding was considered high-risk and high-reward. Additional pilot studies are evaluating computational linguistics and knowledge management tools for biomedical and clinical informatics, portfolio analysis, systems biology, proteomics, genomics, and knowledge representation paradigms. The collective-intelligence initiative will lead to a knowledge infrastructure that can shift the paradigms of data re-use and knowledge discovery dramatically.

- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (I) (CIT, CC, NCI, NHGRI, NIDCR, NIMH, OD)

NIH Federated Identity Service: NIH Federated Identity Service enables people from institutions external to NIH to collaborate by allowing them to use their user name or password from their home organization to access authorized NIH systems. Federated Identity maintains user privacy by keeping the users' credentialing process within their home organization while enabling more seamless collaborations and transactions between federated organizations that can trust each other's identity authentication. Federated Identity Service currently federates with more than 22 institutions, including its sister operational division, the FDA, and universities such as Johns Hopkins, Duke, and Ohio State. NIH made its Clinical & Translational Science Awards (CTSA) Wiki one of the first NIH systems to be federated with nongovernment institutions. Federated Identity facilitates access to the wiki—an online, authorized access, collaborative work environment for members of the CTSA Consortium, which currently supports 1,200 members at 38 universities. The CTSA program reports that 15 of their awarded institutes actively federate with NIH. Other services accepting external credentials through Federated Identity include the website NCCR Annual Progress Report Scientific Information System, FDA ITAS Time and Attendance, NLM NCBI SharePoint for Genome Research, and the Salivary Proteome Wiki. In addition to accepting external accounts, NIH users may use their username and password to access such diverse services as GovTrip, the CTSA Indiana University Wiki, and the Genome Browser at University of California Santa Cruz.

- (I) (CIT)

Large-Scale Informatics Infrastructure

The Cancer Biomedical Informatics Grid® (caBIG®): The caBIG® initiative connects researchers and institutions to enable collaborative research and personalized, evidence-based care. More than 1,500 individuals representing more than 450 government, academic, advocacy, and commercial organizations have collaborated to develop a standards-based grid infrastructure (caGrid) and a diverse collection of interoperable software tools, enabling basic and clinical researchers to speed the translation of information from bench to bedside. Forty-nine of the 65 NCI-designated Cancer Centers and 8 of 10 organizations of the NCI Community Cancer Centers Program are actively deploying caBIG® tools and infrastructure in support of their research efforts. Additionally, caBIG® technology is adapted to power noncancer research initiatives such as the CardioVascular Research Grid. Ongoing collaborations with research and bioinformation organizations in the United Kingdom, China, and India are driving international adoption of caBIG® resources. The caBIG® infrastructure also supports a new health care ecosystem, BIG Health™, in collaboration with various stakeholders in biomedicine (e.g., government, academia, industry, nonprofits, and consumers) in a novel organizational framework to demonstrate the feasibility and benefits of personalized medicine. BIG Health™ will provide the foundation for a new approach in which clinical care, clinical research, and scientific discovery are linked.

Disease Registries, Databases, and Biomedical Information Systems

- For more information, see <http://cabig.cancer.gov>
- For more information, see <http://bighealthconsortium.org/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*
- (E/I) (NCI)

Biomedical Informatics Research Network (BIRN): Modern biomedical research generates vast amounts of diverse and complex data. Increasingly, these data are acquired in digital form, allowing sophisticated and powerful computational and informatics tools to help scientists organize, store, query, mine, analyze, view, and, in general, make better use and sense of their data. Moreover, the digital form of these data and tools makes it possible for them to be shared easily and widely across the research community at large. NIH has supported development of the BIRN infrastructure to share data and tools by federating new software tools or using the infrastructure to federate significant datasets. BIRN fosters large-scale collaborations by using the capabilities of the emerging national cyberinfrastructure. In FY 2009, the BIRN Coordinating Center transitioned to a new home at the University of Southern California. The new BIRN Coordinating Center uses grid computing technology to create a virtual organization for basic and clinical science investigators across the network. In addition, a new BIRN Community Service (U24) grant was awarded to help expand the BIRN user community to researchers and clinicians beyond the neuroscience and imaging fields.

- For more information, see <http://www.ncrr.nih.gov/birn>
- For more information, see <http://www.nbirn.net>
- This example also appears in Chapter 3: *Technology Development*
- (E) (NCRR)

A Clearinghouse for Neuroimaging Informatics Tools and Resources: Many neuroimaging tools and databases are underutilized because they cannot be found easily, are not user-friendly, or are not easily adoptable or adaptable. In an effort to promote the enhancement, adoption, distribution, and evolution of neuroimaging informatics tools and resources, the NIH Blueprint for Neuroscience Research has launched the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC). Examples of included tools are: image segmentation, image registration, image processing pipelines, statistical analysis packages, spatial alignment and normalization algorithms, and data format translators. Resources include: well-characterized test datasets, data formats, and ontologies. Since the first release in October 2007, the clearinghouse website, or NITRC, has become host to 180 tools and resources, with a community of 13,602 unique visitors who downloaded NITRC tools and resources, and 7,000 unique visitors per month, more than 954 of which are registered users (11 percent non-English speaking). The hits to the site have reached 15,635,019/month. Since its inception, more than 50,000 software files have been downloaded. More than 53 percent of the tools on NITRC had not been shared online previously but now are available to the community. In 2009, the NITRC project won the first place of Excellence.gov awards, the largest Federal government award program to recognize the very best in government IT programs, among 61 competitors. Through the initiative, nearly 40 awards have been made to neuroimaging tools and resource developers to enhance the accessibility, interoperability, and adoptability of their existing tools and resources.

- Ardekani BA, Bachman AH. *Neuroimage* 2009;46(3):677-82. PMID: 19264138. PMCID: PMC2674131.
- For more information, see <http://www.nitrc.org/>
- For more information, see <http://neuroscienceblueprint.nih.gov/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*
- (E) (NIH Blueprint, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

National Centers for Biomedical Computing: There are seven NIH Roadmap National Centers for Biomedical Computing (NCBC). Funded as cooperative agreements, these centers collectively cover broad areas of neuroinformatics, functional genomics, image post processing, multiscale modeling, cellular pathways, semantic data integration and ontologies, information networks, cellular networks and pathways, clinical informatics, disease-gene-environment analysis, and clinical decisions support.

- For more information, see <http://ncbcs.org/>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E) (NIGMS, Common Fund - all ICs participate)

Disaster Information Services: A Disaster Information Management Research Center was established in FY 2008 with the aim to facilitate access to disaster information, promote more effective use of libraries and disaster information specialists in disaster management efforts, and ensure uninterrupted access to critical health information resources when disasters occur. A disaster information website provides access to a broad range of emergency preparedness and response information. The Center also collaborates with the Navy National Medical Center, Suburban Hospital, Johns Hopkins Medicine, and NIH CC in the Bethesda Hospital Emergency Preparedness Partnership to provide backup communication systems and develop tools for patient tracking, information sharing and access, and responder training and to serve as a model for hospitals across the Nation. NIH also develops advanced information services and tools to assist emergency responders when disaster strikes. WISER (Wireless Information System for Emergency Responders) was developed for use during hazardous materials incidents and is available on the Internet or for downloading onto PDAs and PCs. Usage continues to grow, with more than 47,000 downloads onto PDAs in FY 2008. Radiation Event Medical Management (REMM) is a downloadable toolkit for use by health care providers during a mass casualty radiation event, with a version for mobile platforms released in FY 2008. Developed in collaboration with the HHS Office of Public Health Preparedness, REMM includes procedures for diagnosis and management of radiation contamination and exposure, guidance for use of radiation medical countermeasures, among other features to facilitate medical responses to radiation emergencies.

- For more information, see <http://disasterinfo.nlm.nih.gov>
- For more information, see <http://wiser.nlm.nih.gov>
- For more information, see <http://remm.nlm.nih.gov>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (I) (NLM)

Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer Care: The purpose of the Cancer Research Network (CRN) is to enhance research on cancer epidemiology, prevention, early detection, and control in the context of health care delivery systems. CRN combines established research groups affiliated with 14 health care delivery organizations that provide comprehensive care to a racially and ethnically diverse population of nearly 11 million individuals. CRN has developed strong research capabilities in several areas: developing and applying innovative methods to collect and interpret data from both conventional and electronic medical records systems; assembling large samples of patients with documentation of patient characteristics and longitudinal data on receipt of health services and clinical and quality-of-life outcomes; collecting and integrating complex data from patients, providers, and organizations to examine issues in health care delivery from multiple perspectives; quantifying the effect of key factors in the delivery process that may determine quality and outcomes of care; and conducting studies on behavioral and systems-based interventions to improve the delivery of care in community-based health care delivery systems. The Breast Cancer Surveillance Consortium (BCSC) is a research resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. The BCSC is a collaborative network of seven mammography registries with linkages to tumor and/or pathology registries. The Consortium's database contains information on 7,521,000 mammographic examinations, 2,017,869 women, and 86,700 cancer cases.

Disease Registries, Databases, and Biomedical Information Systems

- For more information, see <http://crn.cancer.gov>
- For more information, see <http://breastscreening.cancer.gov/>
- This example also appears in Chapter 2: *Cancer*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Clinical and Translational Research*
- (I) (NCI)

CISNET—A Resource for Comparative Effectiveness Research: The Cancer Intervention and Surveillance Modeling Network (CISNET) represents a quantum leap forward in the practice of modeling to inform clinical and policy decisions. While contemporary science has enabled the collection and analysis of health-related data from numerous sectors, enormous challenges remain to integrate various sources of information into optimal decision-making tools to inform public policy. Collaborative work on key questions promotes efficient collecting and sharing of the most important data and critical evaluation of the strengths and weaknesses of each resource. Providing results from a range of models, rather than a single estimate from one model, brings credibility to the process and reassures policymakers that the results are reproducible. CISNET is a consortium of NIH-sponsored investigators who use modeling to improve understanding of the impact of cancer control interventions (e.g., prevention, screening, and treatment) on incidence and mortality trends. The consortium's work informs clinical practice and recommended guidelines by synthesizing existing information to model gaps in available knowledge. CISNET provides a suite of models that are poised to determine the most efficient and cost-effective strategies for implementing technologies in the population. Four groups of grantees focus on breast, prostate, colorectal, and lung cancers using statistical simulation and other modeling approaches. Their models incorporate data from randomized controlled trials, meta-analyses, observational studies, epidemiological studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of these interventions.

- For more information, see <http://cisnet.cancer.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Research*
- (E/I) (NCI)

NIH Biowulf Cluster Enables Large-Scale Biomedical Research: The Biowulf cluster provides NIH researchers with a world-class supercomputer that enables the conduct of large-scale biomedical computational projects, allowing scientific research that otherwise would not be possible. Biowulf comprises more than 6,000 interconnected processors operating cooperatively to solve such diverse problems as: identifying genotype patterns of variation across worldwide human populations; validating algorithms used in computer-aided detection of colon polyps ("Virtual Colonoscopy"); computing the molecular structures of viruses such as HIV using 3D electron microscopy; facilitating whole-genome assembly and genome-wide association studies resulting from next-generation DNA-sequencers; and, as part of the NIH Roadmap Initiative for Molecular Libraries, generating conformation ensembles for 25 million chemical structures. In 2008-2009, more than 105 scientific papers published by NIH intramural scientists cited the use of Biowulf as a computational resource.

- This example also appears in Chapter 3: *Technology Development*
- (I) (CIT)

Biomedical Informatics Research and Training

Informatics Research Training Programs: Exploiting the potential of information technology to augment health care, biomedical research, and education requires investigators who understand biomedicine as well as knowledge representation and decision support. NLM is the principal source of extramural funding for research training in the fields of biomedical informatics, supporting approximately 270 trainees at 18 institutional training programs throughout the country. NLM also provides intramural informatics research training opportunities for another 70 students, postdoctorates, and visiting scientists, as well as training and career development fellowships for health science librarians on the NIH campus and at academic health sciences centers across the country. Collectively, NLM's research training programs

encompass health care informatics, bioinformatics, clinical research translational informatics, and public health informatics. Recent highlights and developments in informatics training include:

- A congressional supplemental appropriation for FY 2008 allowed NIH to add 26 NLM training slots.
- A Diversity Short-Term Trainee Program was implemented to improve the diversity of informatics trainees, with funding for 18 trainees at 7 training programs.
- Funds from the American Reinvestment and Recovery Act were committed to support an additional 56 2-year slots at 10 of its informatics training programs.
- A new Clinical Informatics Postdoctoral Fellowship was established to attract young physicians to NIH to pursue research in informatics.

→ For more information, see <http://www.nlm.nih.gov/training.html>

→ This example also appears in Chapter 3: *Research Training and Career Development*

→ (E/I) (NLM) (ARRA)

Technology Development

By 2030, 72 million Americans will be 65 years old or older. The strain that this population will put on the health care system will be broad-based, but critical care settings in particular—especially intensive care unit (ICUs)—will face significant challenges. ICU care succeeds in part by intensive monitoring of a patient's changing condition. However, keeping track of that level of detail, especially in a busy unit, can slow treatment decisions, and in some cases, lead to errors. A team of NIH-funded researchers sees an opportunity to improve the efficiency, accuracy, and timeliness of clinical decision-making in the intensive care setting. They are developing an ICU patient monitoring system that not only will track vital signs in real time but also will model and predict potential clinical outcomes given various scenarios. Clinicians and researchers also will use this multiparameter intelligent monitoring in intensive care (MIMIC) system as a knowledge base with open access to further develop and test computer models that may improve care.

Introduction

NIH support of technology development continues to trigger revolutions in the understanding of health and disease. In recent years, biotechnology and nanotechnology have undergone extensive technology development. Biotechnology combines disciplines such as genetics, molecular biology, biochemistry, embryology, and cell biology, which in turn are linked to disciplines such as information technology, robotics, and bioengineering to enable the development of new or enhanced tools and devices to further basic scientific research as well as lead to improvements in human health. Nanotechnology research takes advantage of the phenomenon that the properties of some materials change significantly at very small scales, often with surprisingly useful consequences. NIH-supported nanotechnology research exploits this phenomenon in efforts to develop devices with unique features for diagnosing and treating disease. It is a highly multidisciplinary field, drawing from fields such as applied physics, materials science, supramolecular chemistry, and mechanical and electrical engineering.

Examples of FYs 2008 and 2009 NIH-supported technology development research include:

- A microchip to identify cancer cells circulating throughout the body
- "Medical GPS" to navigate through the body, find cancer cells within a tumor, destroy them, and deliver chemotherapy
- Hand and arm prosthesis systems controlled by intact muscle recordings that produce fine finger movements and offer feedback on position and force
- A lensless microscope that fits into a cell phone and assists with remote bedside monitoring
- Innovative high-throughput methods for detecting and characterizing disease-causing alterations in genes and proteins
- A new system of biomaterials that reprograms cells in the body to fight cancer
- Smart coatings for implants that mimic human tissue

Technology development critical to research on a specific disease, organ system, life stage, or field is supported by the relevant NIH Institute. For example, NCI supports the development of technology necessary to more effectively diagnose and treat cancer. NIEHS supports research on how environmental exposures affect human health and actively develops technology that facilitates understanding of how the environment influences the development and progression of human disease.

In addition, NIBIB and NCRR support broad areas of technology development and application, including infrastructure. They also support interdisciplinary research aimed at developing fundamental platform technologies that can be translated into several biomedical applications. This work sometimes is done in collaboration with a disease-specific Institute as the work moves closer to clinical application.

Many of the core challenges in today's research require technologies, databases, and other scientific resources that are more sensitive, robust, and easily adaptable to unique applications than existing technologies. This is especially true in order to develop a more detailed understanding of the vast networks of molecules that make up cells and tissues, their interactions, and their regulation; to develop a more precise knowledge of the combined effects of environmental exposures, individual susceptibility, and molecular events at the onset of disease; and to capitalize on the completion of the human genome sequence and recent discoveries in molecular and cell biology. Moreover, wide access to such tools is important. In 2002, NIH recognized that a gap existed in the support of crosscutting technology development essential to creating such tools. In response, the NIH Roadmap theme New Pathways to Discovery was initiated to advance understanding of biological systems and build a better "toolbox" for medical research in the 21st century. The NIH Roadmap is supporting the development of these resources through five components of the New Pathways to Discovery theme, including Building Blocks, Biological Pathways, and Networks; Molecular Libraries and Molecular Imaging; Structural Biology; Bioinformatics and Computational Biology; and Nanomedicine.

NIH supports technology development through several complementary approaches, including:

- High-risk, innovative projects with very little preliminary indication of the likelihood of success but a potentially significant impact. These projects usually have small budgets and short timeframes, aimed at proof-of-principle.
- Research project grants with a sound basis in preliminary data, directed at development of a particular technology; some projects may take only a few years while others continue for a decade or more.
- Bioengineering research partnerships, which bring together multiple disciplines such as engineering, cell biology, physics, and neurology to develop solutions to specific biomedical questions or diseases.
- Specialized centers that represent a critical mass of expertise and technology, in which multidisciplinary development of complex, often unique technologies is pursued, typically in the context of challenging research problems that cannot be approached with existing tools.
- Small business grants through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs foster highly innovative projects to bring technological advances into the marketplace for the broadest possible availability and impact. These programs allow NIH to leverage the unique resources and perspectives available in the private sector to complement the work done at universities and the NIH intramural program.

Summary of NIH Activities

The research pipeline is replete with examples of NIH's commitment to technology development, its foresight in identifying emerging needs and promising areas of investigation, and its ability to foster the development of technology that links basic research with clinical applications. The following is an overview of technology development activities at NIH.

Diagnostic and Point-of-Care Technologies

Ideally, patients would have access to high-quality and consistent health care regardless of where they live. Realizing this vision necessitates the development of portable, reliable, and inexpensive equipment. To achieve this also will require the leveraging of technologies developed in other fields, such as telecommunications. Advances in fiber-optic and wireless communications devices allow physicians to engage in telemedicine, that is, the transmission via the Internet of medical information, to deliver health care by communicating with other physicians or pathologists thousands of miles away.

NIH currently funds the Point-of-Care Technologies Research Network, a network of four centers that are developing new point-of-care technologies for early and rapid detection of a wide variety of serious conditions such as neurological emergencies, sexually transmitted diseases, multi-pathogen detection for national disaster preparedness, and diagnosis of infections. These technologies are being designed for use in low-resource settings among underserved populations. The network emphasizes collaboration between front-line health care workers and technology developers so that appropriate tools are created to meet clinical needs.

Technology Development

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Point-of-care technologies for use in pathology laboratories, emergency rooms, doctors' offices, and homes will be a key component of the evolving health care system. Current devices, developed largely with NIH support, range from handheld glucose monitoring systems used by diabetics to monitor their blood sugar levels to laptop-sized ultrasound scanners. Among the technologies on the horizon is a lens-free optical microscope about the size of a dime. The device could be inserted into a cell phone and used as a diagnostic device in rural settings or developing countries, for example in diagnosing malaria. The cost of an individual unit would be about \$10.

Another new device has the potential to save eyesight. Born of collaboration between researchers at NIH and NASA, a dynamic light scattering probe detects and quantifies a protein in the eye that is critical to keeping the eye's lens clear. Age-related cataracts develop because too little of the protein, alpha crystallin, is present in the eye. The new probe will be used to monitor the effects of cosmic radiation on astronauts' eyes as well as to study the effects of aging on earth-bound eyes. Early detection of alpha crystallin depletion could lead to treatments that could delay or eliminate the need for cataract surgery.

Although treatment outcomes for primary cancers have improved in the last decade, many deaths occur as a result of the cancer spreading. Body scans can detect distant cancers but often only after the cancer has begun its destructive work. NIH-supported researchers have created a microchip able to detect circulating tumor cells (CTC) in whole blood. This means that from a sample of a patient's blood the microchip identifies specific cancer cells that are spreading through the body via the circulatory system. Clinicians can then make treatment decisions for specific patients based on the molecular and genomic information provided by the CTC analysis.

NIH-supported researchers have created a microchip able to detect circulating tumor cells in whole blood.

E-Health and Biomedical Information Technology

Harnessing the power of the Internet will create unprecedented access to health care information in patient files as well as to raw research data from clinical trials. For health science researchers, shared virtual libraries provide access to data and images from hundreds of studies in various fields. Devising the infrastructure to support a seamless end-user environment requires the collaboration of a host of professionals in computer science, medicine, records management, and other related fields.

NIH-supported efforts are affecting how health care providers, patients, and researchers will use information technology in the future. One such endeavor allows patients to access their own health information. Complete access to diagnostic results and treatment details will permit patients to play an active role in their own health care decision-making by asking more informed questions about their care. Patients will be able to provide this information to any health care provider regardless of where they are located. NIH supports research to ensure that the data are secure during storage and transmission and to address compliance with the Health Insurance Portability and Accountability Act. Benefits of this approach include a reduction in medical errors and elimination of duplicative diagnostic procedures.

Next-generation health care will offer consumers ultrasensitive technologies and techniques to assess normal and diseased states of the body coupled with quick access to vast amounts of health-related data. New modes of collecting patient information, such as the patient-reported outcomes measurement information system (PROMIS), will affect how patients provide information on their conditions and how doctors use that information in treatment decisions. A Web-based computer adaptive testing system, PROMIS will record patient reports on symptoms such as pain, fatigue, and emotional

distress related to various chronic diseases. Other programs that take advantage of the Internet include Positive Choice, a program to reduce risky behaviors that lead to the spread of HIV.

Databases and information clearinghouses are vital tools that allow investigators to streamline their research efforts. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3). The Chemical Effects in Biological Systems (CEBS) Knowledge Base is one such tool that provides data on how different chemicals affect various species. The data, deposited by researchers from industry, government, and academia, assists in understanding how exposures to various substances affect a person's health.

One of the most popular NIH clearinghouses is the Clearinghouse for Neuroimaging Informatics Tools and Resources (NITRC). In the 2 years since its launch, the NITRC has averaged 7,000 visitors per month, provided 50,000 software downloads, and has nearly 1,000 registered users. In 2009, the project won First Place in the Excellence.gov awards, which recognize the very best in government IT programs.

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Another resource for collaborative work is the Cancer Biomedical Informatics Grid® (caBIG®), which offers a wide range of software tools to help basic and clinical scientists translate their findings from laboratory to clinic. The caBIG® approach has been adapted to non-cancer research including the Cardiovascular Research Grid. International partners are assisting in dissemination of the technology worldwide community.

To harness the power of computers, NIH supports the Biowulf cluster, a world-class supercomputer that provides intramural researchers with the ability to conduct large-scale biomedical computational projects. Biowulf comprises more than 6,000 interconnected processors operating cooperatively to solve such diverse problems as identifying genotype patterns of variation across human populations worldwide; validating algorithms used in computer-aided detection of colon polyps in "virtual colonoscopy"; computing the molecular structures of viruses such as HIV using 3-dimensional electron microscopy; facilitating whole-genome assembly and genome-wide association studies resulting from next-generation DNA sequencers; and, as part of the NIH Roadmap Initiative for Molecular Libraries, generating structural information for 25 million chemical structures.

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Gene Sequencing and Beyond

The sequencing of the human genome generated excitement in the scientific community. It gave researchers a new way to analyze the function of cells, tissues, and systems in the body to better understand the causes of disease. As more is learned about the genetic contributions to disease, DNA sequence information will become an important tool for individuals and health care providers to evaluate individualized outlooks for disease risk and to improve the prevention, diagnosis, and treatment of disease. However, to deliver genetic information to individuals on a much wider basis, significant decreases must be made in the cost and time needed to sequence an entire human genome. Rapid gains have been made on this front since the start of the Human Genome Project and costs continue to fall dramatically. NIH supports technology development to make genome sequencing more affordable and genomic information a routine part of health care. For example, NIH-supported researchers are conducting studies to discover the molecular mechanisms underlying complex diseases like addiction, which is strongly influenced by genetics. Investigators studying various neurological and psychiatric illnesses already have linked certain genes with specific diseases using custom screening tools known as "gene

chips." Applying these tools to addiction and other brain disorders advances understanding of not only vulnerability to addiction and its comorbidities, but also of ways to target treatments based on an individual's genetic profile. (Also see the section on *Genomics* in Chapter 3.)

Image-Guided Interventions

To detect disease in its earliest stages, and thereby preempt it before symptoms appear, clinicians will need to examine smaller, more localized areas of the body. Image-guided interventions (IGI)—treatments or procedures that precisely target areas within the body with the aid of imaging techniques such as MRI, computed tomography (CT), or ultrasound—enable clinicians to look beneath the surface anatomy to visualize underlying pathology. As a result, images can be used to navigate the anatomy for biopsy and treatment of disease. In addition to diagnosing at-risk individuals, IGI may offer a safer, less-invasive approach to many surgical procedures. Compared with traditional open surgery, minimally invasive procedures result in less tissue trauma, less scarring, and faster postoperative recovery time, which translates into shorter hospital stays and a more rapid return to family and work.

NIH's new Center for Interventional Oncology is leading the way in developing and disseminating innovative cost-effective alternatives to open surgery. Physicians can navigate through the body using "medical GPS"—real-time imaging such as magnetic resonance, computed tomography, or ultrasound. Once at the desired location, the physician can insert a needle into a tumor, deliver heat to destroy it, and then deposit a drug to wipe out residual cancer cells. The center also is pioneering new image-guided approaches to track personalized responses to new drug therapies over time. These endeavors are contributing to the future of personalized medicine.

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Imaging Biological Systems

Better tools and techniques to understand activities within cells, tissues, and organ systems enable researchers to probe deeper to gain an understanding of the biological systems and networks that control both normal function and diseased states. For example, two NIH intramural research groups are collaborating to develop a next-generation MRI system to examine the human brain. The system uses a 7-tesla magnet to produce highly detailed images that reveal structures not visible using conventional MRI.

More detailed information about the body's internal organs is critical to detecting early stages of disease. Finding new ways of using current MRI systems can advance safer diagnostic methods. In the case of liver disease, biopsies may cause pain, result in missed work, and also carry a risk of bleeding. NIH-supported researchers have developed a non-invasive way to assess the liver using MRI and shear waves, a special type of sound wave. With MRI the researchers capture snapshots of the shear waves as they propagate through liver tissue. A computer program translates the waves into a map of the liver that displays the stiffness of the organ. Stiffness indicates disease while suppleness indicates healthy tissue. This could provide a safer alternative not only for liver biopsy but also for diagnosis of cancer in the breast, prostate, and kidney.

Investments in Infrastructure

Advances in the development of new technology cannot come without supporting the infrastructure that undergirds the research endeavor. To that end, NIH supports a Shared Instrumentation Grant and High-End Instrumentation Program, which provides new generation technologies to groups of NIH-supported extramural investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants.

NIH, through additional funding provided by the American Recovery and Reinvestment Act, also is supporting the improvement of facilities for basic and clinical research around the United States to meet the research, training, and support needs of colleges, universities, and other institutions. The Extramural Research Facilities Improvement Program awards grants to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities for biomedical and behavioral research.

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Insights from Animal Models

Another key tool in discovering how a gene or protein malfunctions and causes disease is the use of animal models of disease. Over the last 25 years researchers have bred countless animals with deliberately altered genes that serve as models for studying normal and disease states. These "transgenic" animal models are assisting in fundamental research for a broad range of diseases and conditions. For example, NIH-supported scientists have developed various animal models of human cancer including breast, colon, lung, and others. These models are being used in cancer drug development to answer fundamental questions of drug pharmacology and toxicity. This knowledge is essential to the design of Phase I clinical trials in which the safety, dose level, and response to a new drug are studied in humans.

The models also provide new insights into serious medical conditions such as sepsis, spinal cord injury, and hearing and balance disorders. Sepsis is a serious medical condition caused by a bacterial infection and is a leading cause of illness and death in the United States and worldwide. New treatments for sepsis are on the horizon because of successful studies in animal models. In one study, NIH-supported researchers induced sepsis in an animal model and then infused the blood with bone marrow stromal cells (known to mediate the body's immune response). The stromal cells weakened the body's inflammatory response, thereby lessening the negative effects of sepsis. This opens up the possibility of preparing and storing stromal cells for patients at risk of developing sepsis.

New treatments for sepsis are on the horizon because of successful studies in animal models.

NIH-supported researchers also are using mouse models to study how injected peptide amphiphiles (molecules with water-soluble and water-insoluble properties) self-assemble into minute fibers (nanofibers) that inhibit glial scar formation following spinal cord injury and promote regeneration of both motor fibers and sensory fibers.

Mouse models of hereditary hearing impairments have been instrumental in mapping and cloning many of the deafness genes in humans. These animal models offer researchers many opportunities to study deafness, hereditary factors involved in hearing loss, and genes that are critical for the development and maintenance of the human ear. (Also see the section on *Molecular Biology and Basic Sciences* in Chapter 3.)

Large-Scale Collaborative Activities

The Biomedical Technology Research Centers (BTRCs) and Biotechnology Resource Centers supported by NIH serve a unique purpose in the broad context of NIH-funded research. They represent a critical mass of technological and intellectual resources with a strong focus on service and training for outside investigators. They develop new technologies and tools in areas including tissue engineering, biomaterials, neural communication technologies, imaging, informatics, synchrotrons, electron microscopy, proteomics and glycomics, optics, lasers, and BioMEMS (microelectromechanical systems—technology just above nano-size—that manipulate, analyze, and measure biological or chemical materials). Access to these technologies is critical to enabling research, yet they are frequently too advanced or expensive to be widely available. In FY 2009 there were approximately 70 of these centers located throughout the country that disseminate

Technology Development

and promote the application of such cutting-edge technologies. These technologies are developed across the full spectrum from bench to bedside. These centers are multidisciplinary and collaborative and serve as catalysts for integrating the diverse efforts of NIH-supported researchers, and providing technological infrastructure, experimental and computational resources, and expertise.

The Biomedical Technology Research Centers and Biotechnology Resource Centers represent a critical mass of technological and intellectual resources. They develop new technologies and tools in areas including tissue engineering, biomaterials, neural communication technologies, imaging, informatics, synchrotrons, electron microscopy, proteomics and glycomics, optics, and lasers.

The goal of the NIH-funded Biomedical Informatics Research Network (BIRN) is to allow researchers to collaborate by sharing data and tools. The BIRN is developing the informatics infrastructure necessary to allow any group of investigators to share data among themselves or with a broader community (also see the section on *Disease Registries and Other Data Systems* in Chapter 3). The resulting collaborative environment extends beyond the boundaries of individual laboratories to enable collaborations that cross geographic and disciplinary boundaries. Basic and clinical investigators are able to share disparate data as well as powerful new analytical tools and software across animal models and among multiple sites. This major initiative was developed to allow neuroimagers to share data and tools, but the infrastructure is generic and therefore applicable to other disciplines.

The goal of the NIH-funded Biomedical Informatics Research Network is to allow researchers to collaborate by sharing data and tools.

The Center for Human Immunology, Autoimmunity, and Inflammation (CHI) is a new trans-NIH intramural initiative designed to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiologies, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease. CHI provides unique specific technologies, including flow cytometry to analyze immune cells; high-throughput systems technologies involving the use of new methods for large-scale examination of biological entities ranging from genes to enzymes; and advanced biostatistical and computer modeling methods. These technologies often are unavailable to individual laboratories because of cost, complexity, and novelty.

Another technology-intensive collaborative endeavor has developed due to the rapid expansion of the dietary supplement marketplace. This expansion has resulted in a proliferation of ingredients and products and has overtaken the development of reliable analytical methods. Precise, accurate, and rugged analytical methods and reference materials are essential for verification of ingredient identity and measuring the amounts of declared ingredients in raw materials and finished products. Also, dietary supplement labels are required to list certain facts about product identity and content and to be truthful and not misleading. That this is not always the case is due, in part, to the lack of proven and agreed-upon methods to precisely assess the quantity of constituents of many supplements and supplement ingredients. NIH's congressionally mandated Analytical Methods and Reference Materials program is intended to assist in providing these critical tools for quality assurance. NIH is partnering with the Food and Drug Administration and the National Institute of Standards and Technology to promote the development, validation, and dissemination of analytical methods and reference materials for commonly used dietary supplement ingredients.

Multidisciplinary and Interdisciplinary Research

Team research offers one of the best environments to develop new technologies and refine current ones. This approach applies principles and methods from the quantitative sciences and engineering to address problems in the biological sciences and medicine. A team of scientists from different disciplines may identify problems and develop innovative

solutions more quickly than a researcher working alone. NIH fosters and cultivates cooperative research so that fundamental discoveries and tools can be developed, even when their specific applications might not be obvious. For example, the laser—originally developed in the physics laboratories studying energy and light—has been adapted to invent microscopes that are critical to many research areas as well as a variety of surgical tools, including systems for laser eye surgery. Continued success in the future will require sustained and strong linkages among engineering, clinical medicine, physical science, computational science, and the biological sciences.

Multidisciplinary teams are essential to solving the complex technological problems that many emerging fields present. NIH-supported investigators studying osteoarthritis are working with imaging researchers to develop new ways of diagnosing and assessing the degeneration of cartilage. Using a relatively new imaging technique, optical coherence tomography, along with MRI, the group hopes to create a new method of visualizing the microstructures found in cartilage. (Optical coherence tomography is a technique for obtaining high-quality, three-dimensional, cross-sectional images of tissues using optical beams.) They are but one of several groups recently awarded grants under the Building Interdisciplinary Research Teams (BIRT) program. The initiative promotes interdisciplinary research backed by strong innovation and high potential benefits to advance study in the areas of arthritis and musculoskeletal and skin diseases.

NIH-supported investigators studying osteoarthritis are working with imaging researchers to develop new ways of diagnosing and assessing the degeneration of cartilage.

Building a better mousetrap often means pooling resources and ideas. Partnerships among engineers, clinicians, scientists, and industrial technologists provide a reservoir of information for NIH investigators. One such partnership is creating innovative technologies to assist war veterans who have damaged or lost limbs as well as civilian amputees and those with spinal cord injuries. A range of electronic and robotic devices will help these individuals stand, move, and step. Especially promising is a new generation of hand and arm prostheses that provide fine finger movement and a sense of touch.

Getting to the moon required input from engineers, physicists, computer scientists, bioscientists, and a host of others. Going back into space for a prolonged stay requires the same collaborative effort. NIH recently paired with NASA to support biomedical experiments that astronauts can perform on the International Space Station (ISS). As a national laboratory, the ISS now provides space to researchers from other Federal agencies, universities, and industry. New experiments on the ISS will examine the effects of microgravity and radiation on biological systems. Molecular and cellular biologists and researchers interested in biomaterials and telemedicine are especially needed to design experiments.

Here on Earth, the interplay of ideas among teams of NIH-supported investigators, including clinicians, biomedical researchers, and electrical and computer engineers, has produced promising techniques to identify mothers at risk for premature delivery. One group used a noninvasive ultrasound approach to assess cervical changes in an animal model weeks before the due date. Another group has developed novel computational tools to analyze uterine biomagnetic signals of term and preterm patients to predict the onset of labor. With an early warning of potential preterm delivery, clinicians may have new tools to fight one of the leading causes of infant death in the United States.

Nanotechnology

A sheet of paper is about 100,000 nanometers thick. The field of nanotechnology deals with matter approximately 1 to 100 nanometers in dimension. At these scales, matter exhibits unusual biological, chemical, and physical properties. By bringing together researchers from physics, material science, and engineering, NIH is developing a powerful cadre of investigators who will use nanotechnology to significantly change how we diagnose and treat disease. One such group has used electrical forces generated at the molecular level to suspend a microscopic object in mid-air. This finding could contribute to the design of tiny machines to perform surgery.

Technology Development

Sharing information across disciplines is critical to nanotechnology research. NIH's Alliance for Nanotechnology in Cancer brings together researchers from biology to oncology. The alliance is building a community of cancer nanotechnologists who develop novel approaches to preventing, diagnosing, and treating cancer and sharing that knowledge with the larger medical community. New nanodevices that quickly and accurately assess proteins and DNA structures implicated in cancer, nanoparticle imaging agents to clearly visualize cancer, and implantable nanosensors to monitor cancer progression will reshape the toolkit clinicians use to fight cancer.

NIH's Alliance for Nanotechnology in Cancer brings together researchers from biology to oncology, building a community of cancer nanotechnologists who develop novel approaches to preventing, diagnosing, and treating cancer and sharing that knowledge with the larger medical community.

Oversight for nanotechnology research falls to the Trans-NIH Nanotechnology Task Force, a body established to discover new avenues of study at the nexus of nanotechnology, nanomedicine, and nanobiology as well as to examine the human health effects of engineered nanomaterials. NIH has been named the Government's lead agency for coordination of Federal research on the health implications of nanotechnology under auspices of the National Nanotechnology Initiative's Nanoscale Science, Engineering, and Technology Subcommittee (NSET) and plays a key role in development of its Environmental, Health, and Safety Strategy.

Probing Proteins

Information resulting from the Human Genome Project is now helping scientists as they begin to study proteins, the tiny powerhouses within cells responsible for cell function. By visualizing protein structures, researchers gain a better understanding of many of the biochemical processes related to health and disease. This information also can be used to design drugs that target specific parts of a bacteria, virus, or tumor.

As a result of the NIH-sponsored Protein Structure Initiative (PSI), investigators now have a more potent set of tools to examine the protein in three dimensions. By the end of October 2009, PSI-supported researchers had identified more than 4,000 protein structures. In 2009, NIH announced plans for a new phase of the program—PSI: Biology. During the PSI: Biology phase, highly organized networks of investigators will apply the new paradigm of high-throughput protein structure determination, which was successfully developed during the earlier phases of the PSI, to study a broad range of important biological and biomedical problems. The initiative will make resources for high-throughput structure determination available to a larger community of scientists than has been engaged to date. The majority of targets for structure determination will be defined through consortium partnership arrangements and an open, ongoing community nomination process. Additional targets will be defined through biological theme projects of the structure determination centers.

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Structural biology is a field in which scientists learn about molecules by determining their 3-D structures in atom-by-atom detail. Large user facilities called synchrotrons allow researchers to use X-rays to determine molecular structures more easily, quickly, and cheaply than ever before. NIH funded the development of a new experimental station at the Advanced Photon Source at Argonne National Laboratory. The new station includes three X-ray beamlines for use by scientists from across the United States to determine the detailed, three-dimensional structures of molecules, which will lead to improved understanding of basic biological processes and for drug design.

Transforming Health Care

The combination of new tools and techniques developed to improve basic research as well as those aimed at delivering better health care will transform the current medical paradigm in response to 21st century needs. Health care of the future will include innovations such as neural interfaces to help paralyzed individuals; approaches that will enable diagnostic tests and therapeutic treatment to be administered simultaneously (theranostics); and improvements in the health, quality of life, and productivity of older individuals. NIH-supported researchers are leading the way toward a new paradigm in which technology is a central feature of fast and effective health care delivery. NIH funding of technology development provides an environment that enables investigators to think beyond what is conventional, to do so across disciplines, and to take the health care system to a level that will engage scientists, patients, and physicians in a collaborative experience.

Neural interfaces are systems that operate at the intersection of the nervous system and an internal or external device, including neural prosthetics. Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. NIH pioneered the development of this technology, beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants that help people with hearing impairments, respiratory and hand grasp devices for people with spinal cord injuries, and deep brain stimulation for Parkinson's disease, among other contributions. Current work aims to restore voluntary bowel and bladder control and standing to spinal cord injured persons, allow paralyzed persons to control devices directly from their brains, improve cochlear implants, and improve deep brain stimulation, which may be applicable to many brain disorders. Through the years, this program has fostered the development of a robust research community, now including private sector companies, and represents a cooperative effort between NIH, the Department of Veterans Affairs, and the Department of Defense.

Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. NIH pioneered the development of this technology.

NIH is leading the way in the development of new technologies to provide both disease diagnosis and treatment simultaneously. The concept of combining a therapeutic with a diagnostic agent is rapidly evolving and goes beyond traditional diagnostic tests that screen or confirm the presence of a disease. With specialized molecular imaging techniques and biomarkers, tailored and personalized medicine approaches could predict risks of disease, diagnose disease, and monitor therapeutic response leading to real-time, cost-effective treatment. NIH supports a number of teams that are developing theranostics that can be applied in clinical studies of human patients. A team of chemists and neurosurgeons at the University of Michigan is developing highly specific, dye-loaded nanoparticles capable of delivering targeted photosensitizers to improve the survival of brain tumor patients. These particles also contain imaging contrasting agents to visualize response to therapy. This technique will allow neurosurgeons to visualize the brain tumors for surgical resection of the main tumor mass while eradicating remaining tumor cells through a process known as photodynamic therapy.

A team of chemists and neurosurgeons at the University of Michigan is developing highly specific, dye-loaded nanoparticles capable of delivering targeted photosensitizers to improve the survival of brain tumor patients.

As the baby boomer generation continues to celebrate milestone birthdays, improving the health of older Americans is more important than ever. To that end, NIH supports 13 Edward R. Roybal Centers whose objective is to improve the health, quality of life, and productivity of middle-aged and older people by facilitating translation of basic behavioral and social science to practical outcomes by developing new technologies and stimulating new "use-inspired" basic research in the behavioral and social sciences. Roybal investigators have made several key discoveries. For example, researchers have developed tools and technologies for identifying older adults at risk for automobile crash involvement, and are working with industry partners to develop and disseminate products based on these tools. Additionally, researchers have developed

a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Other companies have used this model to develop related products, and the model has spurred several new grant-funded research projects, including the development of a new medication tracker for older adults.

On many fronts, NIH-supported technology development is making a difference in how we approach both wellness and disease. This knowledge, in turn, will help to improve the quality of life for all.

Notable Examples of NIH Activity

Key

E = Supported through Extramural research
 I = Supported through Itramural research
 O = Other (e.g., policy, planning, or communication)
 COE = Supported via congressionally mandated Center of Excellence program
 GPRA Goal = Government Performance and Results Act
 ARRA = American Recovery and Reinvestment Act
 IC acronyms in **bold** face indicate lead IC(s).

Diagnostics and Point-of-Care Technology

Point-of-Care Technologies: Testing at the point of initial contact, or point-of-care (POC), rather than at specialized centers or hospitals uses state-of-the-art diagnostics and information systems that can be used in the doctor's office or even at home. Consequently, the use of POC devices also can help patients monitor their wellness in preventive medicine. The POC approach to health care delivery can significantly improve the quality and reduce the cost of health care by: providing earlier diagnosis of disease when treatment is more effective and less costly; making modern medicine available to those who lack access to regular care, such as people in rural settings or developing countries; combining cutting-edge diagnostic and communication technologies to bring patients into more frequent and regular contact with health care providers; and enabling a patient-centered process with home-based monitoring. To address the challenges of health care quality and accessibility, NIH currently funds a network of four Centers that targets the development of new POC technologies for early and rapid detection of strokes, detection of sexually-transmitted diseases, rapid multi-pathogen detection for national disaster readiness, and diagnosis of infections, which can be used in low-resource settings among underserved populations. A major characteristic of the network is to facilitate clinical/technology interactions so that user-specific information can be shared with technology developers who typically lack relevant clinical connections. In 2009, the network funded several collaborative exploratory development projects through clinical need-based solicitations in their respective areas.

- For more information, see <http://www.nibib.nih.gov/Research/POCTRN>
- (E) (**NIBIB**)

Low-Cost, Lens-Free Optical Microscope: The optical microscope is used widely in biological and biomedical research. Since the days of van Leeuwenhoek, the image magnification has been based on lenses. This research explores an innovative design of a lens-free microscope. Images are acquired by direct projection imaging of specimens that flow past the imager in microfluidic channels. Using the innovative design concepts, the microscope device has been fabricated in a package of the size of a dime. Early estimation of the fabrication cost of the optofluidic microscope suggested that such devices can be made very inexpensively at about \$10 per unit. This lensless compact microscope can be integrated readily into a point-of-care diagnostic device for applications dealing with rural and global health care

challenges. Large numbers of the compact device can be assembled together for massively parallel imaging of large populations of cells and microorganisms.

- Cui X, et al. *Proc Natl Acad Sci* 2008;105:10670-5. PMID: 18663227. PMCID: PMC2488383.
- For more information, see <http://www.nibib.nih.gov/HealthEdu/eAdvances/30Apr09>
- (E) **(NIBIB)**

A New Imaging Device for Early Detection of Cataract: A transparent ocular lens is essential to vision. Cataract (clouding of the lens) remains the primary cause of blindness in the world today. Age-related cataract, the most common type of cataract, is caused by abnormal aggregation of lens proteins that clouds the lens. In the last few years, it has been established that a particular lens protein, alpha crystallin, prevents other lens proteins from aggregating and probably plays a major role in preventing cataract formation. Humans are born with a fixed amount of alpha crystallin, so age-related cataracts occur when the supply is depleted. Researchers at NIH and NASA collaborated to develop a new imaging device that allows clinicians to detect and quantify the amount of unbound alpha crystallin protein in a patient's eye. The device uses dynamic light scattering to measure the amount of alpha crystallin remaining in the lens. This may lead to a better understanding of the early stages of protein aggregation before cataracts form that impinge on vision. Early detection of lens protein disruption may provide clues to preventive treatments that could delay the need for cataract surgery.

- Datiles MB, et al. *Arch Ophthalmol* 2008;126(12):1687-93. PMID: 19064850. PMCID: PMC2600622.
- For more information, see <http://archophth.ama-assn.org/cgi/content/full/126/12/1687>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (I) **(NEI)**

Microchip Captures Early Circulating Cancer Cells: Malignant cancers shed cells that enter the circulation, travel to other areas of the body, and often grow into secondary tumors, or metastases. Indeed, metastases are responsible for the great majority of cancer deaths. It is estimated that 70,000 men per year are diagnosed with recurrent prostate cancer after prostatectomy, as shown by rising prostate surface antigens. For these men, the ability to detect and characterize the malignant cells in the blood may enable personalized therapy. Researchers are developing a technology to facilitate quantitative detection of circulating tumor cells (CTCs). They have engineered a microchip with a large surface area of an adhesion molecule that binds CTCs from whole blood, making detection of CTCs more reliable than previous approaches. They are analyzing molecular and genomic information in the CTCs to identify new biomarkers to customize treatments that are personalized for the patients and to predict treatment outcomes. The NIH-supported research has the potential to eliminate or greatly reduce cancer deaths due to metastases.

- Nagrath S, et al. *Nature* 2007;450(7173):1235-9. PMID: 18097410.
- For more information, see <http://www.nibib.nih.gov/HealthEdu/eAdvances/31July08>
- This example also appears in Chapter 2: *Cancer*
- (E) **(NIBIB)**

A Test for Taste: Altered taste function has a tremendous impact on food choice, diet, and overall nutritional status. The loss of taste (and smell) impacts the appreciation of food and the desire to eat. This loss exposes an individual to a variety of health risks, including gastrointestinal disorders, heart disease, and diabetes. The true prevalence of taste disorders is not known because scientists lacked a validated taste test that is suitable for large-scale population studies. Such a taste test must be easy to use and can be completed in less than 10 minutes. NIH-supported scientists have adapted a product developed for the food industry (the edible taste strip) to measure human taste capabilities. The precise amount of tastant (sweet, sour, salty, bitter, or savory) can be dissolved in the taste strip, and the strip can be placed in various regions of the mouth (e.g., tongue or palate). The edible taste strip is a sensitive test suitable for the clinic setting to aid the physician

during an examination of an individual who is experiencing problems with their sense of taste. The taste strip can also be used in epidemiological studies for individuals of different ages to establish normative data on the prevalence of taste problems in the general population. This simple, reliable taste test now provides an invaluable diagnostic tool to assess taste function, and, in combination with a smell test, can evaluate chemosensory function.

- Smutzer G, et al. *Laryngoscope* 2008;118(8):1411-6.
- (E) (NIDCD)

E-Health and Biomedical Information Technology

Multiparameter Intelligent Monitoring in Intensive Care: NIH is funding a team of investigators to develop and evaluate an advanced intensive care unit (ICU) patient monitoring system. The system is designed to substantially improve the efficiency, accuracy, and timeliness of clinical decision-making in intensive care. The investigators are gathering data from ICU medical information systems, hospital medical information systems, and bedside ICU monitors. The project has collected approximately 30,000 patient records for the clinical database as well as ICU monitor data for about 5,000 of these patients for the waveform database. The databases have implemented sophisticated de-identification methods, which they developed, so that the data they collect can be reused by others. For example, they have replaced all dates in the records with surrogate dates. Future work will include the development of innovative algorithms and clinician interfaces based on the need for information extracted from this extensive data set.

- For more information, see <http://mimic.mit.edu/>
- For more information, see <http://physionet.mit.edu/physiobank/database/mimic2db/>
- For more information, see <http://www.nibib.nih.gov/HealthEdu/eAdvances/31May09>
- (E) (NIBIB)

Health Information Technology: Health information technology research that enables the integration of clinical data and medical image diagnostic and treatment data with the patient's medical history in a comprehensive electronic medical record will improve clinical decision-making. The ability to connect and exchange diagnostic information and medical images between health care providers, clinics, and hospitals will help provide the timely information that is needed for effective health care and will help reduce unnecessary, excessive, and duplicative procedures. A patient-centered approach to comprehensive electronic health records will allow patients access to their health information. This will enable patients to play an active role in their own wellness by enabling them to ask knowledgeable questions about treatment options. Additionally, patients also are empowered to provide this information to any and all health care providers as needed, independent of their location or where the medical data was created or stored. NIH supports research in new methods and technologies to address issues such as: interoperability of data systems, compatibility of computer software across medical institutions, security of data during transmission, HIPAA compliance, availability of affordable data systems for patient care providers, and integration of medical decision-support information in medical data systems.

- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E) (NIBIB, NLM)

Health IT Standards and Electronic Health Records: NIH researchers are engaged in developing Next Generation electronic health records (EHRs) with advanced decision-support capabilities to facilitate patient-centered care, clinical research, and public health. As the central coordinating body for clinical terminology standards within HHS, NIH works closely with the Office of the National Coordinator for Health Information Technology (ONC) to support nationwide implementation of an interoperable health information technology infrastructure. NIH develops or licenses key clinical terminologies that are designated as standards for U.S. health information exchange. The Unified Medical Language System Metathesaurus, with more than 8.1 million concept names from more than 125 vocabularies, is a distribution

mechanism for standard code sets and vocabularies used in health data systems. NIH also produces RxNorm, a standard clinical drug vocabulary; supports the LOINC nomenclature for laboratory tests and patient observations; and collaborates with the International Health Terminology Standards Development Organisation to promote international adoption of the SNOMED CT clinical terminology. In FY 2009, NIH released the first version of the CORE Problem List Subset of SNOMED CT, designed to facilitate coding of problem list data in EHRs by mapping frequently used terms from seven large-scale health care institutions to corresponding SNOMED CT concepts. The Newborn Screening Codes and Terminology Guide, a Web portal to support more effective use of newborn screening laboratory test information, was created in FY 2009 in collaboration with ONC, the Health Resources and Services Administration, and newborn screening organizations.

- For more information, see <http://www.nlm.nih.gov/research/umls>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (NLM)

Patient-Reported Outcomes Measurement Information System (PROMIS): The PROMIS initiative is developing new ways to measure patient-reported outcomes (PROs) for clinical research, such as pain, fatigue, physical functioning, emotional distress, and social role participation, which have a major impact on quality of life across a wide variety of chronic diseases. The first phase of PROMIS successfully has addressed its initial broad objectives of developing and testing a large item (survey question) bank for measuring PROs, along with translation of certain items into Spanish; creating a computer adaptive testing (CAT) system that allows for efficient, scientifically robust assessment of PROs in patients with a spectrum of chronic diseases; and producing a publicly available, Web-based system that continues to be updated and modified, to allow clinical researchers access to PROMIS resources, such as a common repository of validated items, a CAT system, and hard copy surveys. Preliminary results demonstrate that a short, 10-item PROMIS survey, administered by CAT, outperforms the most commonly used, paper-based, self-reporting assessment tool for arthritis disability (the Health Assessment Questionnaire). These results are indicative of the anticipated advantages of the PROMIS tool: better answers with fewer patients. The success of the project has garnered 4 more years of NIH funding for PROMIS. Prioritized tasks for PROMIS include validating and evaluating usability in future NIH-supported clinical trials, including Spanish translations; developing additional modes of administration; facilitating adoption of PROMIS by the clinical research community; and building partnerships to secure long-term sustainability for the PROMIS tools.

- For more information, see <http://nihroadmap.nih.gov/clinicalresearch/overview-dynamicoutcomes.asp>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIAMS, Common Fund - all ICs participate)

Using the Web to Broaden the Delivery of Effective Treatments: NIH is testing the efficacy of delivering evidence-based psychosocial interventions for drug abuse and HIV prevention via the Web or other computer-based media, while assessing their relative cost and efficacy compared to more traditional delivery formats. Variables of interest include abstinence, treatment retention, health risk, quality of life, and social outcomes. New research shows that computer-based training for cognitive behavioral therapy appears to have both short-term and enduring effects on drug use—that is, fewer days of drug use for many months following treatment compared to controls. Another computer-based intervention, called Positive Choice, was tested in HIV-positive patients as a means of reducing risky behaviors that lead to HIV spread. Five San Francisco clinics participated, exposing patients to a "video doctor" to conduct a risk assessment and risk reduction counseling program. Patients waiting to see the provider use a laptop computer to watch video clips and respond by means of a color-coded keyboard. That, too, was successful, and sharply reduced sexual and drug risk behaviors in HIV-positive patients. These delivery methods stand not only to greatly increase cost effectiveness of interventions, but to provide a means for broader dissemination, including to those in remote locations where therapists may not be available. Our research will continue to investigate how such interactive technology can be integrated to improve the addiction treatment system and bring about more widespread adoption of evidence-based approaches.

- For more information, see <http://ajp.psychiatryonline.org/cgi/content/full/165/7/>
- For more information, see <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0001988>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDA)

A Clearinghouse for Neuroimaging Informatics Tools and Resources: Many neuroimaging tools and databases are underutilized because they cannot be found easily, are not user-friendly, or are not easily adoptable or adaptable. In an effort to promote the enhancement, adoption, distribution, and evolution of neuroimaging informatics tools and resources, the NIH Blueprint for Neuroscience Research has launched the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC). Examples of included tools are: image segmentation, image registration, image processing pipelines, statistical analysis packages, spatial alignment and normalization algorithms, and data format translators. Resources include: well-characterized test datasets, data formats, and ontologies. Since the first release in October 2007, the clearinghouse website, or NITRC, has become host to 180 tools and resources, with a community of 13,602 unique visitors who downloaded NITRC tools and resources, and 7,000 unique visitors per month, more than 954 of which are registered users (11 percent non-English speaking). The hits to the site have reached 15,635,019/month. Since its inception, more than 50,000 software files have been downloaded. More than 53 percent of the tools on NITRC had not been shared online previously but now are available to the community. In 2009, the NITRC project won the first place of Excellence.gov awards, the largest Federal government award program to recognize the very best in government IT programs, among 61 competitors. Through the initiative, nearly 40 awards have been made to neuroimaging tools and resource developers to enhance the accessibility, interoperability, and adoptability of their existing tools and resources.

- Ardekani BA, Bachman AH. *Neuroimage* 2009;46(3):677-82. PMID: 19264138. PMCID: PMC2674131.
- For more information, see <http://www.nitrc.org/>
- For more information, see <http://neuroscienceblueprint.nih.gov/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E) (NIH Blueprint, NCCAM, NCCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

The Cancer Biomedical Informatics Grid® (caBIG®): The caBIG® initiative connects researchers and institutions to enable collaborative research and personalized, evidence-based care. More than 1,500 individuals representing more than 450 government, academic, advocacy, and commercial organizations have collaborated to develop a standards-based grid infrastructure (caGrid) and a diverse collection of interoperable software tools, enabling basic and clinical researchers to speed the translation of information from bench to bedside. Forty-nine of the 65 NCI-designated Cancer Centers and 8 of 10 organizations of the NCI Community Cancer Centers Program are actively deploying caBIG® tools and infrastructure in support of their research efforts. Additionally, caBIG® technology is adapted to power noncancer research initiatives such as the CardioVascular Research Grid. Ongoing collaborations with research and bioinformation organizations in the United Kingdom, China, and India are driving international adoption of caBIG® resources. The caBIG® infrastructure also supports a new health care ecosystem, BIG Health™, in collaboration with various stakeholders in biomedicine (e.g., government, academia, industry, nonprofits, and consumers) in a novel organizational framework to demonstrate the feasibility and benefits of personalized medicine. BIG Health™ will provide the foundation for a new approach in which clinical care, clinical research, and scientific discovery are linked.

- For more information, see <http://cabig.cancer.gov>
- For more information, see <http://bighealthconsortium.org/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (NCI)

NIH Biowulf Cluster Enables Large-Scale Biomedical Research: The Biowulf cluster provides NIH researchers with a world-class supercomputer that enables the conduct of large-scale biomedical computational projects, allowing scientific research that otherwise would not be possible. Biowulf comprises more than 6,000 interconnected processors operating cooperatively to solve such diverse problems as: identifying genotype patterns of variation across worldwide human populations; validating algorithms used in computer-aided detection of colon polyps ("Virtual Colonoscopy"); computing the molecular structures of viruses such as HIV using 3D electron microscopy; facilitating whole-genome assembly and genome-wide association studies resulting from next-generation DNA-sequencers; and, as part of the NIH Roadmap Initiative for Molecular Libraries, generating conformation ensembles for 25 million chemical structures. In 2008-2009, more than 105 scientific papers published by NIH intramural scientists cited the use of Biowulf as a computational resource.

- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (CIT)

Informatics Training for Global Health: As biomedical information has increased exponentially in recent years, computer-based tools have been developed to access and analyze this information and to aid the process of research design, data management, and data analysis. The sheer volume of data generated in many biomedical and behavioral research projects and in clinical trials can no longer be managed effectively without electronic help. Further, access to computers and the Internet is becoming commonplace in research institutions throughout the developing world. To take advantage of these tools, individuals with the advanced skills to use them are critically needed. However, despite the central role informatics plays in global health, many low and middle income country (LMIC) institutions have very few informatics experts and a very weak information technology infrastructure. There is a critical need to train local experts who are able to develop local research applications or modify existing platforms to provide tools that are appropriate for the needs, culture, and infrastructure of their institutions and countries. In response, NIH's Informatics Training for Global Health program aims to develop human capital to meet global health challenges, to support the development of research hubs in LMICs, and to bolster the development of expertise in the use of information and communication technologies in support of research and research training.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-09-001.html>
- This example also appears in Chapter 3: *Research Training and Career Development*
- (E) (FIC, NHGRI, NIBIB, NLM)

Children and Clinical Studies: Medical research in children has saved lives and improved health and well-being, yet parents often are reluctant or uncertain about allowing their child to participate in a clinical study. The Children and Clinical Studies campaign helps parents and others to learn more about how clinical research is conducted in children, so that they can make well-informed decisions about whether to participate. Its website, which is available in English and Spanish, combines practical information with award-winning video footage of parents, health care providers, and children themselves discussing the rewards and challenges of participating in research. Educational materials for parents and health care providers can be requested through the site, as well.

- For more information, see <http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (NHLBI, NCCR, NICHD)

Technology Development

Gene Sequencing and Beyond

Medical Sequencing: As more is learned about the genetic contributions to disease, DNA sequence information will become even more important for providing medically relevant information to individuals and their health care providers. When it becomes practical to sequence each patient's genome, genetic information will be used to provide more individualized outlooks of disease risk and improve the prevention, diagnosis, and treatment of disease. NHGRI's medical sequencing program, initiated in 2006, aims to drive continued improvement in DNA sequencing technologies and to produce data important to biomedical research. Seven studies are currently underway to identify the genes responsible for several relatively rare disorders and to survey the range of gene variants that contribute to certain common diseases.

- For more information, see <http://www.genome.gov/15014882>
- This example also appears in Chapter 3: *Genomics*
- (E, I) (NHGRI)

Genome Technology and the \$100,000 and \$1,000 Genome Initiatives: Taking the discoveries made in genetic research initiatives and delivering them to patients on a much wider basis will require significant decreases in the cost and time needed to sequence an entire human genome. Rapid gains have been made on this front since the start of the Human Genome Project and costs continue to fall dramatically. However, it still remains prohibitively expensive to sequence the genomes of individual patients in the clinic. Developing technology to make genome sequencing more affordable is essential for making genomic information part of routine medical care. NIH's Genome Technology program supports research to develop rapid, low-cost methods, technologies, and instruments that will:

- Read DNA sequences
- Check sequences for genetic variations (SNP genotyping)
- Aid research to understand the effects of genetic variations on genomic function.

In 2004, NIH began funding research to develop technologies specifically intended to lower the cost of sequencing the amount of DNA in a human genome, about 3 billion base pairs. These efforts include:

- "Near-Term Development for Genome Sequencing" Grants. These awards support research to enable the sequencing of a human-sized genome for about \$100,000.
- Revolutionary Genome Sequencing Technologies Grants. These awards aim to develop breakthrough technologies that will enable an individual's genome to be sequenced for \$1,000 or less.

- For more information, see <http://www.genome.gov/10000368>
- For more information, see <http://www.genome.gov/27527585>
- This example also appears in Chapter 3: *Genomics*
- (E) (NHGRI)

New Genetics/Epigenetic Tools Shed Light on Addiction: NIH-supported research is taking full advantage of expanding databases and fast technologies to identify links between genetic variations and disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms underlying complex diseases like addiction, which genes strongly influence. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as "gene chips" (e.g., the neurexin gene has been found to play a role in drug addiction). Applying these tools to addiction and other brain disorders advances our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient's genetic profile. To complement these efforts, NIH is investing in the equally important field of epigenetics, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to

epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the deleterious long-term changes to brain circuits from drug abuse. For example, using a powerful new technique known as ChIP-on-chip to monitor epigenetic changes correlated with gene activity, investigators have recently mapped the genomic effects of chronic cocaine use in the reward center of the mouse brain. Such analyses provide needed information about which genes are altered by cocaine and can point to new targets for medications development. Epigenetic discoveries can also inform ways to smartly alter environmental factors so as to decrease the risk for drug abuse and addiction.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-015.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-016.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-003.html>
- For more information, see <http://nihroadmap.nih.gov/epigenomics/initiatives.asp>
- For more information, see <http://nihroadmap.nih.gov/commonfundupdate.asp>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*
- (E/I) (NIDA, NCI, NIAAA, NIMH) (GPRA)

Image-Guided Interventions

Development of Image-Guided Interventions: Image-guided interventions (IGI) provide therapy that can minimize trauma and improve patient outcomes. They are applicable in procedures such as biopsy, surgery, radiation treatment, vascular interventions, and guidance during delivery of devices, drugs, cells, or genes. These improved capabilities particularly are important in light of the shifting trend in medicine toward a model of early, presymptomatic detection of disease. Representative of ongoing research is an effort to improve image-guided surgical removal of tissue using optical coherence tomography (OCT). Recent studies suggest that OCT optical imaging techniques may have a significant impact on breast cancer biopsy and treatment. High-resolution OCT image guidance could help ensure complete surgical removal of tumors and adequate diagnostic biopsy sampling. As other biomedical imaging modalities, such as MRI, improve the ability to detect small suspicious lesions, OCT can be used to guide a biopsy needle precisely to tumor tissue and cells and enable sampling of these smaller nonpalpable lesions. In preliminary studies, surgically removed lumpectomy specimens from more than 65 patients have been imaged with OCT in the operating room. When compared to post-operative histopathology, OCT yielded a sensitivity of 100 percent and a specificity of 82 percent and demonstrates the potential of OCT as a real-time method for the intraoperative margin assessment in breast-conserving surgeries.

- Nguyen FT, et al. Meeting Abstract: Optical coherence tomography (OCT) as a diagnostic tool for the real-time intraoperative assessment of breast cancer surgical margins. *Cancer Res* 2009;69: 802.
- This example also appears in Chapter 2: *Cancer*
- (E) (NIBIB) (GPRA)

Image-Guided, Minimally Invasive Interventions: Image guidance offers a cost-effective, safe, and less invasive approach to many common diseases. From treating a uterine fibroid, a brain aneurysm, or cancer, image-guided minimally invasive interventions are ushering in an era of personalized and cost-effective alternatives to open surgery. Diagnosis and therapy often are poorly integrated, creating a gap in health care delivery. NIH support of technology development has enabled physicians to better use medical imaging during minimally invasive procedures, not solely for pre- or post-procedure diagnosis. The unique translational environment of the NIH CC has enabled interdisciplinary and trans-agency development and dissemination of novel cost-effective approaches. This includes navigation with "Medical GPS" for tumor ablation, whereby a "smart" needle is inserted with image guidance into a tumor to heat and kill cancer cells. The heat also deploys nanoparticles at the site of the tumors that are engineered specially to deploy their chemotherapy cargo where needed to avoid systemic toxicities. Such drug + device + imaging combination therapies were pioneered by NIH as part of an inter-agency, multi-IC, and industry-academic partnership. Using prior images during later invasive procedures

Technology Development

makes the procedures targeted and personalized, without requiring the expensive imaging equipment to be brought physically to the procedure room. Imaging also has been used to guide energy (high-intensity focused ultrasound) through the skin, to the level of the inner disease process to kill tissue or to deposit drugs in a targeted fashion.

- For more information, see <http://www.cc.nih.gov/centerio/index.html>
- For more information, see <http://www.cc.nih.gov/drd/irlab/index.html>
- For more information, see <http://www.cancer.gov/ncicancerbulletin/061609/page4>
- (I) (CC, NCI, NHLBI, NIBIB)

Imaging Biological Systems

High Resolution Anatomical and Functional Imaging of the Human Brain: NINDS and NIMH Intramural Research Programs are partnering to push the frontiers of MRI (magnetic resonance imaging) of the human brain and to make these developments available to researchers. The NINDS Laboratory of Functional and Molecular Imaging has led development of the next generation MRI device that uses a powerful 7T (Tesla) magnet, compared to the usual 1.5T magnetic strength. Overcoming the many technical challenges of imaging at 7T has yielded extraordinarily detailed images, which have contrast and spatial resolution as much as 100 times better than previous methods. These images reveal structures never before seen in the living human brain that may be critical in detecting early stages of disease. The NIMH functional MRI core facility serves more than 30 principal investigators on the NIH Bethesda campus and leads development of functional brain imaging. The facility has played a major role in making 3T MRI widely available for routine use. Together NINDS and NIMH investigators have pioneered imaging methods that increase the detail of structural and functional changes that investigators can detect in the brain, while improving time resolution and shortening duration for brain scans. A two-step strategy to continue this successful program will first translate 7T MRI from its present prototype design to routine use and then develop one of the world's first 11.7T MRI devices for imaging the human brain. Increased MRI resolution will improve diagnosis and monitoring of neurological and psychiatric disorders and open new opportunities for understanding brain function.

- For more information, see http://intramural.nimh.nih.gov/fmri/fmri_research.html
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (I) (NINDS, NIMH)

Feeling Organs with Imaging: MRI is known for providing exquisite anatomical images of internal organs. Using a new technique that involves imaging while pushing on an organ with sound waves, researchers are able to feel the stiffness of internal organs. Because tumors often are more stiff than normal tissue (think, for example, of feeling for a "lump" of stiffer tissue in the breast), this technique may provide important diagnostic information about disease. Initially, this technique is being used to examine the stiffness of liver and potentially provide an alternative to liver biopsy for the 170 million individuals worldwide who live with chronic hepatitis C, a major cause of liver disease.

- Venkatesh SK, et al. *AJR Am J Roentgenol* 2008;190:1534-40. PMID: 18492904.
- Yin M, et al. *Magn Reson Med* 2007;58:346-53. PMID: 17654577.
- Yin M, et al. *Clin Gastroenterol Hepatol* 2007;5:1207-13. PMID: 17916548. PMCID: PMC2276978.
- Kruse SA, et al. *Neuroimage* 2008;39:231-7. PMID: 17913514. PMCID: PMC2387120.
- For more information, see <http://www.nibib.nih.gov/HealthEdu/eAdvances/28Aug08>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIBIB)

NCI Imaging Programs: In addition to their applications in basic scientific discovery, imaging technologies contribute to cancer care through contributions to screening, diagnosis, disease staging, treatment guidance, treatment monitoring, and detection of cancer recurrence. NCI's imaging programs include the extramural Cancer Imaging Program (CIP), whose mission is to promote and support basic, translational, and clinical research in imaging sciences, and several intramural efforts within the Center for Cancer Research (CCR), such as the Molecular Imaging Program, Radiation Biology Branch, Radiation Oncology Branch, Center for Interventional Oncology, and NCI-Frederick Small Animal Imaging Program. The National Lung Screening Trial (NLST) is comparing two ways of detecting lung cancer: spiral computed tomography (CT) and standard chest X-ray. Both chest X-rays and spiral CT scans have been used to find lung cancer early. So far, neither chest X-rays nor spiral CT scans has been shown to reduce a person's chance of dying from lung cancer. This study will aim to show if either test is better at reducing deaths from this disease.

- For more information, see <http://imaging.cancer.gov>
- For more information, see <http://home.ccr.cancer.gov/connections/features2.asp>
- For more information, see <http://www.cc.nih.gov/centerio/index.html>
- For more information, see <http://web.ncifcrf.gov/rtp/lasp/intra/saip/>
- For more information, see <http://www.cancer.gov/NLST>
- This example also appears in Chapter 2: *Cancer*
- (E/I) (NCI) (GPRA)

Simulating and Analyzing Musculoskeletal Dynamics: NIH-funded investigators have introduced OpenSim, a freely available open-source simulation platform to accelerate the development and sharing of simulation technology and to integrate dynamic simulations into the field of movement science, in particular animal and human neuromusculoskeletal systems. OpenSim tools allow one to edit muscles, analyze dynamic simulations, and track motions, a process that enables accurate muscle-driven simulations to be generated that represent the dynamics of individual subjects. OpenSim is being developed and maintained on Simtk.org, which is a software development environment that is being developed under the parent Roadmap Simbios National Center for Biomedical Computing.

- Liu MQ, et al. *J Biomech* 2008;41(15):3243-52. PMID: 18822415.
- (E) (NIGMS)

Molecular Imaging Probe Development Program Review: An emerging biomedical technology with great potential for improving disease diagnosis and treatment is molecular imaging. However, molecular imaging techniques still are used primarily for preclinical applications. The transfer of these preclinical tools into clinical tools remains a demanding problem and requires the development of novel molecular imaging probes that have increased sensitivity and specificity, and are nontoxic. Approaches to developing more sensitive and specific nontoxic probes were discussed and developed at a Molecular Imaging Program Progress Review that was held on May 19, 2008, in Bethesda, MD. The panel identified high-priority areas that would advance future research in the molecular imaging field, and, in particular, would be capable of translation to clinical applications. The report of this panel discussion was posted on the NIBIB website and provided to the National Advisory Council for Biomedical Imaging and Bioengineering for further strategic planning in this area.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-09-016.html>
- (O) (NIBIB)

Investments in Infrastructure

Shared Instrumentation Grant and High-End Instrumentation Programs: The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained

Technology Development

through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the \$100,000-\$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the \$750,000-\$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located at core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2008, the SIG program funded a total of 82 grants for \$30,623,406; the HEI funded a total of 20 awards for \$33,309,434. In FY 2009, NIH received \$300 million in ARRA funding to provide shared instrumentation to extramural researchers through the SIG and HEI programs. To best serve the needs of NIH-supported investigators, the range of HEI awards funded by ARRA was expanded and now is \$600,000 to \$8 million.

- For more information, see <http://www.ncrr.nih.gov/btinstruments>
- For more information, see <http://www.ncrr.nih.gov/recovery>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E) (NCR) (ARRA)

Extramural Construction Program Expands Research Capacity: The American Recovery and Reinvestment Act (ARRA) provided \$1 billion to NIH for the Extramural Construction program. The program will build capacity to conduct biomedical and behavioral research by supporting the costs of improving non-Federal basic research, clinical research, and animal facilities to meet the research, research training, or research support needs of institutions. One component of the program, the Extramural Research Improvement Program, awards grants to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities for biomedical and behavioral research. Another component of the program, the Core Facility Renovation, Repair, and Improvement activity, awards grants to public and nonprofit private entities to renovate, repair, or improve core facilities. A core facility is a centralized shared resource that provides access to instruments or technologies or services, as well as expert consultation to investigators supported by the core. Institutions apply for construction grants by submitting applications, which are selected using NIH's standard, competitive, peer-reviewed process. Funding decisions are based on the scientific and technical merit of the application as determined by first and second level of peer review, the availability of funds, the relevance of the application to NIH program priorities, the national geographic distribution of awards, and the priorities specified in the ARRA, such as energy efficiency and job creation. The objective of the ARRA Extramural Construction program aligns with the objective of the existing Research Facilities Improvement Program, which is also administered by NIH.

- For more information, see <http://www.ncrr.nih.gov/recovery/construction>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E) (NCR) (ARRA)

ARRA-Funding Expands Research Capabilities: NCR is using its ARRA funds designated for scientific research to accelerate the Center's research priorities and support research, resources, tools, and training to help researchers funded by NIH transform basic discoveries into improved human health. In contrast to most of the NIH ICs that fund primarily Research Project Grants (i.e., R01s), NCR primarily supports large Center programs that build research capacity and offer training and career development. Consistent with NCR's research portfolio, a few previously reviewed Research Project Grants (R01s and R21s) are being awarded with ARRA funds. Through competitive revision awards, NCR is encouraging NIH-funded researchers (primarily supported by other NIH ICs) to leverage the resources, expertise, and infrastructure of NCR centers and Center-like programs. To further advance the scientific progress of NCR programs, administrative supplements are being awarded to: advance translational (pre- and post-clinical) research, achieve CTSA

consortium strategic goals, enhance NCRR pilot project mechanisms, promote collaborative community engagement research, improve research workforce development, and strengthen science education and dissemination. A new ARRA-supported initiative will develop infrastructure to connect people and resources across the Nation and promote interdisciplinary collaborations and scientific exchange. Additional ARRA funding is supporting NIH-led activities such as the Challenge Grants and the Summer Research Experiences for Students and Science Educators. From the beginning of the ARRA-funding strategy development, NCRR leadership decided to align its ARRA activities broadly with the goals and objectives of the NCRR 2009-2013 Strategic Plan.

- For more information, see <http://www.ncrr.nih.gov/recovery>
- For more information, see http://www.ncrr.nih.gov/strategic_plan/implementation/
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
- (E) (NCRR) (ARRA)

Electronic Scientific Portfolio Assistant: Demand for information about program performance and results, as well as accountability and transparency, continues to increase across the Federal government. The Electronic Scientific Portfolio Assistant (e-SPA) offers a comprehensive means by which to conduct statistically meaningful portfolio analyses of program performance. The development of e-SPA grew out of program needs to ensure accountability and transparency of information about program performance and results. Though e-SPA was developed initially for NIAID program managers, it quickly has become a valuable analysis tool across NIH. e-SPA provides extramural program directors with the capability to monitor, analyze, and compare the performance of their research portfolios and individual investigators. The tool generates user-defined portfolios of research projects and links the projects to outcome indicators including funding, publications, citations, impact factors, inventions, and patents. e-SPA uses information available from multiple databases to enhance synthesis and analysis of relevant data, and provides data visualization capability through a dashboard and graphs.

- (O) (NIAID)

Insights from Animal Models

New Biomaterials System Programs Cells in situ to Fight Cancer: In the body's immune response to foreign invaders, dendritic cells signal and activate other cells to initiate a generalized inflammatory response. Cell-based cancer vaccinations build on this natural tendency by isolating and activating a patient's dendritic cells using tumor antigens, and then injecting the reprogrammed cells back into the patient. The activated dendritic cells travel home to the lymph nodes and promote an antitumor response. Unfortunately, most transplanted dendritic cells die. Additionally, reprogrammed cells partially lose their effectiveness after injection back into the body. Thus, multiple rounds of injections are required to achieve significant effect. To address these limitations, investigators developed a multifunctional in situ dendritic cell reprogramming system composed of polymeric biomaterials that release cytokines to attract dendritic cells already within the lymph nodes into the biomaterials. The dendritic cells are then activated by the biomaterials. The biomaterials reduce their cytokine release at a controlled rate so that after activation, the dendritic cells will migrate away from the biomaterials back home to the lymph nodes and present tumor antigens to T cells found there. In a mouse model this sophisticated system provided protection from tumor development equal or superior to that provided by traditional cancer vaccines without the complications and costs of ex vivo cell manipulation and transplantation. The new system also provided much better control over the number of dendritic cells than traditionally generated cancer vaccines. This study demonstrates a powerful new application for polymeric biomaterials that could be used in the future against cancers and other diseases.

Technology Development

- Ali OA, et al. *Nature Materials* 2009;8(2):151-8. PMID: 19136947. PMCID: PMC2684978.
- This example also appears in Chapter 2: *Cancer*
- (E) (NIDCR)

New Model Reveals Novel Molecular Strategies in the Fight to Overcome Oral Cancer: Oral and pharyngeal carcinomas are the ninth most common cancer worldwide, with more than 35,000 new patients and more than 7,500 deaths each year in the United States alone. The 5-year survival rate has improved only marginally over the past 40 years. There is an urgent need for new options for these patients. Emerging information on the deregulation of normal molecular mechanisms that result in the cancer's progression provides the possibility of new mechanisms-based therapeutic approaches for these aggressive oral malignancies. NIH scientists recently used a two-step chemical carcinogenesis model and found that the drug rapamycin exerted a remarkable anticancer activity. It decreased the tumor burden of mice having early and advanced tumors, and even brought about the regression of recurrent squamous cell skin cancers. The scientists reported that the persistent activation of mTOR, the mammalian Target of Rapamycin, occurs frequently in head and neck cancer patients and that its inhibition by rapamycin causes regression of human oral cancer tumors implanted in mice. Because chemically induced animal cancer models often better reflect the complexity of the clinical setting, the scientists developed an oral-specific chemical carcinogenesis mouse model. In this model, activation of mTOR is an early event in precancerous lesions; rapamycin treatment can halt the malignant conversion of precancerous lesions and promote the regression of advanced carcinogen-induced oral squamous cell carcinomas (SCCs). Significance: The development of this SCC carcinogenesis model demonstrates that the use of mTOR inhibitors may provide a novel molecular-targeted strategy for chemoprevention and treatment of oral squamous cell cancer.

- Amornphimoltham A, et al. *Clin Cancer Res* 2008;14(24):8094-101. PMID: 19073969.
- Czerninski R, et al. *Cancer Prevention Res* 2009;2(1):27-36. PMID: 19139015.
- For more information, see <http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/OralCancer/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Research*
- (I) (NIDCR)

Bone Marrow Stromal Cells Help Fight Sepsis: Sepsis is a serious medical condition that affects 18 million people per year worldwide, and is characterized by a generalized inflammatory state caused by bacterial infection. Widespread activation of inflammation and blood clotting pathways leads to multiple organ failure, collapse of the circulatory system (septic shock), and death. In the last few years, it has been discovered that bone marrow stromal cells (BMSCs, also known as mesenchymal stem cells) are potent modulators of immune responses. In this study, BMSCs were administered before or shortly after inducing sepsis by puncturing the intestine to determine whether BMSCs injected into the circulation would have a beneficial effect in preventing or attenuating septic shock. Infusion of BMSCs significantly decreased sepsis-induced mortality and increased organ function in an animal model. The effects appear to be mediated by the production of Prostaglandin E2 when BMSCs are activated during the early stages of sepsis. Prostaglandin E2 subsequently induces the recipient's macrophages to produce substantially more IL-10, a factor that dampens the inflammatory response, which if left unabated, leads to death. This is the first determination of a mechanism by which BMSCs modulate the immune response in an animal model of sepsis. As many people die of sepsis annually as die from heart attacks. A new treatment or preventative regimen desperately is needed. Since the animal model suggests that the BMSCs need not be isolated from the same individual as will receive them, it is possible that cells isolated from nonrelated donors could be prepared and stored for use in patients with high risk for sepsis.

- Nemeth K, et al. *Nat Med* 2009;15(1):42-9, PMID: 19098906. PMCID: PMC2706487.
- For more information, see <http://www.nature.com/nm/journal/v15/n1/abs/nm.1905.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Molecular Biology and Basic Research*
- (I) (NIDCR)

Bioactive Nanostructures for Neural Regeneration: Spinal cord injury (SCI) often leads to permanent paralysis and loss of sensation below the site of injury because of the inability of damaged axons to regrow across the injury site in adults. Nanomaterials built from a family of self-assembling molecules may offer hope for treating serious injuries, such as spinal cord injury according to new results from NIH research. Recently, an NIH-supported research group developed peptide amphiphile (PA) molecules that self-assemble in vivo into supramolecular nanofibers and tested them on mouse models of spinal cord injury. In this work, in vivo treatment with the PA nanofibers, after SCI, reduced cell death and promoted regeneration of both motor fibers and sensory fibers through the lesion site. Treatment with the PA also resulted in significant behavioral improvement. These observations demonstrate that it is possible to inhibit glial scar formation and to facilitate regeneration after SCI using bioactive three-dimensional nanostructures displaying high densities of neuroactive epitopes on their surfaces.

- Tysseling-Mattiace VM, et al. *J Neurosci* 2008;28(14):3814-23. PMID: 18385339. PMCID: PMC2752951.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIBIB)

Using Mice to Examine Hearing and Balance Disorders: Mouse models of hereditary hearing impairment have been instrumental in mapping and cloning many deafness genes in humans. These animal models offer researchers many opportunities to study deafness, hereditary factors involved in hearing loss, and genes that are critical for the development and maintenance of the human ear. For example, the varitint-waddler mouse exhibits hearing loss due to a mutation in the *Trpml3* gene that encodes the protein, TRPML3, which is responsible for mechanosensory conduction within the inner ear. Mutations in the *Trpml3* gene cause disorganization of the stereocilia bundle of sensory hair cells in the inner ear, which ultimately leads to hearing loss. The senses of hearing and balance are highly dependent on the structure of the stereocilia bundles. In this study, NIH intramural scientists, in collaboration with scientists in the United Kingdom, used immunofluorescence to locate the *Trpml3* protein in the base of developing and growing auditory hair cell stereocilia. This study identifies *Trpml3* as a critical channel in maintaining the base of the bundle during stereocilia maturation, which appears to be necessary to establish a functioning stereociliary hair bundle. Mouse models of hearing impairment are important tools to unravel the molecular basis of hearing. They also, in many instances, faithfully mimic the pathophysiology and genetics of human hearing impairment, thus providing animal models to explore the mechanism of action.

- van Anken AF, et al. *J Physiol* 2008;586(Pt 22):5403-18. PMID: 18801844. PMCID: PMC2655368.
- (I) (NIDCD)

Researchers Discover Why Mammalian Teeth Form in a Single Row: Why do mammals develop a single row of teeth whereas other vertebrates, such as sharks, can develop multiple rows of teeth? Researchers studying mutations in the genes of mice that develop teeth serving no apparent function may have solved the mystery. Most of the mutations under study caused the mice to develop the extra teeth within the space between the normal incisor and the normal first molar. Since tooth buds normally develop within this part of the developmental field but later regress, these genetic alterations did not alter the normal plane within which teeth developed. However, one particular mutation had a different result. The researchers found that a knockout mutation (i.e., elimination) of a gene known as Odd-skipped related 2 (*Osr2*) also resulted in the production of extra teeth, but strikingly, these teeth developed outside the usual plane, on the tongue side of the normal molars, suggesting that the mutation results in an expansion of this developmental field in the affected mice. Supporting this theory, the knockout mice (i.e., mice lacking *Osr2*) have spatially expanded expression of other genes involved in tooth development. That suggests that normal *Osr2* acts to restrict tooth development to within its usual, single-row plane. Previous work from this group discovered the *Osr2* gene and demonstrated that it is a novel regulator of palate formation. The current study demonstrates that *Osr2* function also is critical to the patterning of tooth formation and

Technology Development

sheds light on the restriction of teeth to a single row in mammals. Osr2 function may be an important consideration for researchers seeking to grow replacements eventually for lost teeth in adults.

- Zhang Z, et al. *Science* 2009;323:1232-4. PMID: 19251632. PMCID: PMC2650836.
- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/CurrentSNIB/March/SingleRow.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDCR)

Large-Scale Collaborative Activities

Biomedical Technology Research Centers (BTRCs): The BTRCs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Centers and through intensive collaborations with other leading laboratories. The BTRCs are used annually by nearly 5,000 scientists from across the United States and beyond, representing more than \$700 million of NIH funding from 22 ICs. As an example, optical technologies enable researchers to:

- Harness the power of light to "see" biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

- For more information, see http://www.ncrr.nih.gov/biomedical_technology
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E) (NCRR)

Biomedical Informatics Research Network (BIRN): Modern biomedical research generates vast amounts of diverse and complex data. Increasingly, these data are acquired in digital form, allowing sophisticated and powerful computational and informatics tools to help scientists organize, store, query, mine, analyze, view, and, in general, make better use and sense of their data. Moreover, the digital form of these data and tools makes it possible for them to be shared easily and widely across the research community at large. NIH has supported development of the BIRN infrastructure to share data and tools by federating new software tools or using the infrastructure to federate significant datasets. BIRN fosters large-scale collaborations by using the capabilities of the emerging national cyberinfrastructure. In FY 2009, the BIRN Coordinating Center transitioned to a new home at the University of Southern California. The new BIRN Coordinating Center uses grid computing technology to create a virtual organization for basic and clinical science investigators across the network. In addition, a new BIRN Community Service (U24) grant was awarded to help expand the BIRN user community to researchers and clinicians beyond the neuroscience and imaging fields.

- For more information, see <http://www.ncrr.nih.gov/birn>
- For more information, see <http://www.nbirn.net>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E) (NCRR)

Center for Human Immunology, Autoimmunity, and Inflammation: The Center for Human Immunology, Autoimmunity, and Inflammation (CHI) is a new trans-NIH intramural initiative designed to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiology, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease. The Center provides unique specific technologies often unavailable to individual laboratories because of cost, complexity, and novelty. The core of CHI is made up of three technology centers. The first center features assays of immune cells and their products, based mainly on a technique known as flow cytometry and similar emerging techniques. The second center contains high-throughput systems technologies, involving the use of new methods for large-scale examination of genes, proteins, enzymes, and/or lipids. It also features advanced biostatistical and computer modeling methods for mining these diverse data sets, thereby providing for a deeper understanding of immune function and pathology. The third center is based in protocol development, with staff dedicated to producing methods that efficiently translate to the clinic while considering all of the ethical and regulatory requirements for human research.

- For more information, see <http://www.nhlbi.nih.gov/resources/chi/index.htm>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*
- (I) (NIAMS, NCI, NHLBI, NIAID, NICHD, NIDDK, NINDS)

Analytical Methods and Reference Materials (AMRM) Program: The rapid expansion of the dietary supplement marketplace has resulted in a proliferation of ingredients and products and overtaken the pace of development of reliable analytical methods. Precise, accurate, and rugged analytical methods and reference materials are essential for verification of ingredient identity and measuring the amounts of declared ingredients in raw materials and finished products. Also, dietary supplement labels are required to list certain facts about product identity and content and to be truthful and not misleading. That this is not always the case is due in part to the lack of proven and agreed-upon methods to precisely assess the quantity of constituents of many supplements and supplement ingredients. NIH's congressionally mandated AMRM program is intended to assist in providing these critical tools for quality assurance. The program promotes development, validation, and dissemination of analytical methods and reference materials for commonly used dietary supplement ingredients. Responding to concerns about the quality and accuracy of standards and methods used by testing laboratories to measure vitamin D in the body, NIH, in collaboration with the National Institute of Standards and Technology, has developed a new Standard Reference Material (SRM) for vitamin D in blood serum to help laboratories evaluate their analytical methods. This SRM represents a first step toward standardization of vitamin D testing.

- For more information, see http://dietary-supplements.info.nih.gov/Research/Analytical_Methods_and_Reference_Materials_Program.aspx
- (E) (ODP/ODS, ORWH)

National Centers for Biomedical Computing: There are seven NIH Roadmap National Centers for Biomedical Computing (NCBC). Funded as cooperative agreements, these centers collectively cover broad areas of neuroinformatics, functional genomics, image post processing, multiscale modeling, cellular pathways, semantic data integration and ontologies, information networks, cellular networks and pathways, clinical informatics, disease-gene-environment analysis, and clinical decisions support.

- For more information, see <http://ncbcs.org/>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E) (NIGMS, Common Fund - all ICs participate)

Technology Development

Glycomics Technology Development, Basic Research, and Translation into the Clinic: Glycans are ubiquitous complex carbohydrates found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules is thus critical for basic and clinical research across the spectrum of health and disease, but widely is regarded as one of the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- Biomedical Technology Research Centers develop and share cutting-edge technologies for analysis of carbohydrates in complex biological systems.
- Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.
- Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
- A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.

→ For more information, see <http://www.ncrr.nih.gov/glycomics>

→ For more information, see <http://www.functionalglycomics.org>

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*

→ (E) (NCRR, NCI, NHLBI, NIGMS, NINDS)

Multidisciplinary and Interdisciplinary Research

Building Interdisciplinary Research Teams (BIRT) Awards: The scale and complexity of biomedical research demands that scientists move beyond the confines of their individual disciplines and explore new organizational models for team science. Integrating different disciplines holds the promise of opening scientific avenues of inquiry and, in the process, potentially forms new disciplines for addressing increasingly complex questions. The BIRT award was created by NIH to promote interdisciplinary research by supplementing collaborations with high innovation and potentially high impact in general areas of arthritis, musculoskeletal, and skin biology and diseases. In 2008, 11 grants were awarded for the following areas of collaboration: developmental biology—systems biology, soft tissue biology—imaging technologies, tissue engineering—immunology, and tissue engineering—developmental biology.

→ For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2008/birt.asp

→ For more information, see http://www.niams.nih.gov/Funding/Funding_Opportunities/Supported_Scientific_Areas/Musculoskeletal_Diseases/birt_faq.asp

→ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-08-001.html>

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*

→ (E) (NIAMS)

Prostheses to Restore Lost Function: Many veterans return home with significant injuries to their extremities, including loss of limbs. Through multidisciplinary partnerships between engineers, clinicians, scientists, and industrial partners, NIH investigators are developing new and novel technology for assistive rehabilitation, such as electrodes for neural and muscular recordings, networked implantable systems for functional electrical stimulation, robotics for rehabilitation, and brain computer interface systems for communication and control. For example, next-generation hand and arm prosthesis systems controlled by intact muscle recordings will be able to produce fine finger movements and provide to the user the

sensation of position and force applied to an artificial hand. Other examples include multifunctional stimulation systems that allow spinal cord-injured subjects to change posture, stand, step, and control hand and arm function.

- Weir RF, et al. *IEEE Trans Biomed Eng* 2009;56(1):159-71. PMID: 19224729.
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIBIB)

Stem Cells and Regenerative Medicine: Stem cells are able to renew themselves and generate progeny that differentiate into more specialized cells. They play critical roles in organism development, and some are essential for normal homeostasis and tissue repair. NIH has made a significant investment in stem cell research. One NIH-supported study showed that the sex of cells in a subpopulation of muscle-generating stem cells in adult mice can influence their capacity to repair tissue considerably. This finding could lead to future therapies for various diseases, including muscular dystrophy. A collaboration between NIH Intramural researchers and those at Walter Reed Army Medical Center discovered that waste tissues from surgery, removed to promote healing of orthopaedic injuries and war-traumatized muscle, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells. They could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest cells. NIH has partnered with the Department of Defense on an initiative to speed treatments to wounded soldiers abroad, and civilian trauma victims and burn patients in the United States. This collaboration has resulted in the establishment of the new Armed Forces Institute of Regenerative Medicine (AFIRM). The AFIRM-led program will focus on regrowing fingers, repairing shattered bones, and restoring skin to burn victims with genetically matched skin, to pave the way for commercial products in the near future. Hair follicles are useful models for organ regeneration. Recent discoveries have been made in the molecular processes that govern the growth of hair follicle stem cells, which are a source for newly formed hair follicles.

- Deasy BM, et al. *J Cell Biol* 2007 Apr 9;177(1):73-86. PMID: 17420291. PMCID: PMC2064113.
- Jackson WM, et al. *J Tissue Eng Regen Med* 2009 Feb;3(2):129-38. PMID: 19170141.
- Plikus MV, et al. *Nature* PMID: 18202659. PMCID: PMC2696201.
- Horsley V, et al. *Cell* 2008 Jan 25;132(2):299-310. PMID: 18243104. PMCID: PMC2546702.
- Nesti LJ, et al. *J Bone Joint Surg Am* 2008;90(11):2390-8. PMID: 18978407. PMCID: PMC2657299.
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cell_sex_and_stem_cell.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/progenitor_cells.asp
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NIAMS, NIA, NIAID, NIBIB)

Cooperation in Space-Related Health Research: In FY 2009, NIH and the National Aeronautics and Space Administration (NASA) issued a funding opportunity announcement to support biomedical experiments that astronauts could perform on the International Space Station (ISS). The ISS provides a special microgravity and radiological environment that Earth-based laboratories cannot replicate. Congress, recognizing the immense promise the facility holds for American-led science and technology efforts, opened the U.S. portion of the ISS to other Federal agencies and university and private sector researchers when it designated the U.S. resources as a National Laboratory in 2005. Recently published ISS experiments from investigators supported by NIH and NASA have offered new insights into how bacteria cause infectious disease. The FY 2009 solicitation is the next step in a partnership to apply the National Laboratory to research that complements NASA's space exploration efforts. The program encourages a new cadre of health researchers from a variety of disciplines to incorporate the space environment into their experiments, and will support them as they prepare their experiments for launch and analyze their data following a mission. Applications particularly are encouraged

Technology Development

from researchers who are interested in molecular or cellular biology, biomaterials, or telemedicine. NIH expects to fund applications in FY 2010, FY 2011, and FY 2012, and to send experiments into space by 2011.

- Wilson JW, et al. *Proc Natl Acad Sci U S A* 2007;104(41):16299-304. PMID: 17901201. PMCID: PMC2042201.
- For more information, see http://www.niams.nih.gov/News_and_Events/NIH_NASA_Activities/default.asp
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIAMS, NCI, NCR, NHLBI, NIA, NIAAA, NIBIB, NICHD, NINDS)

Researchers Developing a Noninvasive Ultrasound Technique to Detect Early Signs of Premature

Delivery: Premature delivery is one of the leading causes of infant mortality in the United States, according to CDC. Currently, clinicians only can attempt to delay delivery once the extensive uterine contractions of labor have been initiated in the final stages of the delivery process. However, because the cervix prepares for delivery weeks to months before labor in a process termed "preterm cervical ripening," an NIH-supported scientist, together with a team of electrical and computer engineers, theorized that a noninvasive ultrasound technique might be used to detect this early warning sign well in advance of premature delivery. The research team developed and tested such a technique using computer simulations in rat tissue samples, followed by studies with live rats. The results were promising in that cervical changes clearly were identifiable using this technique in the tissue samples. With further development, this innovative technique could prove powerful in identifying mothers at risk for premature delivery, thereby reducing or preventing the associated morbidity and mortality.

- Bigelow TA, et al. *J Acoust Soc Am* 2008;123(3):1794-800. PMID: 18345867. PMCID: PMC2637349.
- For more information, see <http://www.ncbi.nlm.nih.gov/pubmed/18345867>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NINR)

Facilitating Interdisciplinary Research via Innovation in the Behavioral and Social Sciences: An NIH Roadmap Funding Opportunity Announcement (FOA), Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences, was released. Using a modified Exploratory/Developmental (R21) mechanism, this FOA solicits applications to develop new and innovative measures, methods, and technologies that support the integration of human social and/or behavioral science with other disciplines across varying levels of analysis. Supported projects have included: creation of tools to measure sun exposure and vitamin D, models of spinal cord injury, and an Internet-based system for providing feedback to teachers and consultants on the school readiness and mental health of children. Several national conferences have been planned in relation to this initiative, including *Facilitating Interdisciplinary Research: Methodological and Technological Innovation in the Behavioral and Social Sciences* (October 2009).

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-004.html>
- For more information, see <http://nih.blhtech.com/roadmap09/>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDA, OBSSR, Common Fund - all ICs participate)

Interdisciplinary Research Consortia Funded by the NIH Roadmap: One of the four main initiatives established by the NIH Roadmap's Interdisciplinary Research Work Group was a grant program to fund large-scale consortia to support interdisciplinary research. In total, NIH funded nine collaborative teams located across the United States. Each focuses on a particular health problem or process, including substance abuse and stress; obesity; developmental disorders; the process of aging; providing fertility options for cancer survivors; engineering healthy tissue to treat diabetes, heart disease and oral/craniofacial disorders; psychiatric disorders; drug/medications development; and genome engineering. The initial

results suggest ways in which this team science approach helps to increase cooperation within and between academic institutions, as well as advancing the individual missions of NIH ICs.

- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/>
- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp>
- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/members.asp>
- For more information, see <http://nihroadmap.nih.gov/>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E, O) (NIDCR)

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

- Lai M, et al. *Nanotechnology* 2009;20(18):185602. PMID: 19420618.
- Schwartz DE, et al. *Biosens Bioelectron* 2008;24(3):383-90. PMID: 18515059. PMCID: PMC2572081.
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- Lin YY, et al. *Anal Chim Acta* 2008;612(1):23-8. PMID: 18331854.
- Wang J, et al. *Small* 2008;4(1):82-6. PMID: 18081131.
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- Hsu PY, et al. *Cancer Res* 2009;69(14):5936-45. PMID: 19549897. PMCID: PMC2855843.
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- Sridhar S, et al. *BMC Genomics* 2008;9:259. PMID: 18513428. PMCID: PMC2435556.
- Bharate SB, et al. *Bioorg Med Chem Lett* 2009;19(17):5101-4. PMID: 19640713. PMCID: PMC2728166.
- Li B, et al. *Toxicol Sci* 2009;107(1):144-55. PMID: 18930948. PMCID: PMC2638647.
- Nagy JO, et al. *Bioorg Med Chem Lett* 2008;18(2):700-3. PMID: 18086524. PMCID: PMC2839895.
- For more information, see <http://www.gei.nih.gov/exposurebiology/index.asp>
- (E) (NIEHS, NIDDK) (GPRA)

Technology Development

Nanotechnology

Researchers Levitate Object at a Microscopic Scale: Technique May Assist With Development of

Nanotechnology: Similar to the way that like poles of magnets repel each other, certain combinations of molecules generate electrical forces that will prevent them from coming in contact with each other under certain conditions. Building on these concepts, researchers actually have levitated an object, suspending it without the need for external support. Working at the molecular level, the researchers relied on the tendency of certain combinations of molecules to repel each other at close contact, effectively suspending one surface above another by a microscopic distance. In their study, the researchers brought a tiny gold-plated sphere in contact with a flat glass surface, separating them with a liquid known as bromobenzene. At close distances, the molecular forces of the two surfaces, when in the presence of bromobenzene, repelled each other, so that the molecules of gold and glass never came in direct contact with each other and were separated by a few nanometers. The new technique may prove useful to the emerging field of nanomechanics—the development of microscopic machinery and even robots. By altering and combining molecules, tiny machines and even robots could be devised to perform surgery, manufacture food and fuel, and boost computing speed, operating free of friction.

- Munday JN, et al. *Nature* 2009;457(7226):170-3. PMID: 19129843.
- For more information, see <http://www.nichd.nih.gov/news/releases/jan07-09-Levitate-Object.cfm>
- (I) (NICHD)

Nanotechnology in Cancer: Nanotechnology innovation has been driven predominantly by physicists, engineers, and chemists; progress in cancer research comes primarily from discoveries of biologists and oncologists. The NIH Alliance for Nanotechnology in Cancer has set a goal of creating a community of cancer nanotechnologists who work together to develop nanotechnology approaches; apply them to the prevention, diagnosis, and treatment of cancer; and educate the medical community about opportunities enabled by cancer nanotechnology. The Alliance organized a session at 2009 American Association for Cancer Research meeting on Cancer Diagnostics Using Nanotechnology Platforms. Participants included high-profile investigators who work on the development of new nanodevices for in vitro diagnosis and in vivo imaging and clinicians who define oncology applications of those devices. Examples of this work include: PRINT, a technique allowing for controllable fabrication of nanoparticles; researching novel diagnostic techniques for proteins and DNA; developing implantable nanosensors; researching novel nanoparticle-based imaging agents and nanosensors; and developing nanotechnology-based cancer screening tools.

- For more information, see <http://nano.cancer.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NCI)

Nanotechnology Task Force: Nanotechnology deals with the understanding and control of matter at dimensions of approximately 1 to 100 nanometers, where unique phenomena enable novel applications. By applying cross-disciplinary methods from physics, material science, and engineering, NIH is shaping a new paradigm with vast implications for revolutionizing diagnostics, therapeutics, and personalized medicine. NIH initiated the Trans-NIH Nanotechnology Task Force for the purpose of (a) identifying scientific opportunities at the interface of nanotechnology, nanomedicine, and nanobiology; and (b) enhancing understanding of the health implications of engineered nanomaterials (ENMs) for biological systems. The Task Force tracks NIH investments in basic and applied nanoscale research, organizes national and international meetings, develops reports, participates in congressional hearings, and plays a key collaborative role in interagency activities. NIH has been named the Federal government's lead agency for coordination of Federal research on the health implications of nanotechnology under auspices of the National Nanotechnology Initiative's Nanoscale Science, Engineering, and Technology Subcommittee (NSET) and plays a key role in development of its Environmental, Health, and Safety Strategy.

- For more information, see <http://dpcpsi.nih.gov/collaboration/>
- (O) (OSP/OSPA, FIC, NCI, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)

Tracking Stem Cell Mobility Within Cardiovascular Tissues: Current cellular therapies suffer from low rates of cell engraftment due to the early destruction of cells. In 2007, in response to a program announcement, Innovative Application of Nanotechnology to Heart, Lung, Blood, and Sleep Disorders, NIH funded a grant to formulate a biocompatible cell encapsulation agent designed to protect and track mesenchymal stem cells for administration to patients. (Mesenchymal stem cells are the progenitors of all connective tissue cells). The investigators have demonstrated that encapsulation of mesenchymal stem cells improves long-term cell viability in cultures, and also have shown that the encapsulated cells can be detected using computed tomography or magnetic resonance imaging following in vivo injection. NIH is assessing the progress of the grant through an ongoing GPRA goal—by 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.

- (E) (NHLBI)

Probing Proteins

Protein Structure Initiative (PSI): Scientists learn a lot by studying the detailed, three-dimensional structures of proteins. This knowledge helps them better understand the biochemical processes involved in health and disease. It also can greatly advance the design of medicines to treat a wide range of diseases. Recognizing this, NIH established PSI in 2000 to determine the structures of hundreds of novel proteins by means of high-throughput structure determination. In 2009, NIH announced plans for a new direction of the Protein Structure Initiative to be named PSI:Biology. The new program will support research partnerships between groups of biologists and high-throughput structure determination centers to solve problems of biomedical importance. In addition to benefiting the PSI team, this work will continue to accelerate research in other fields.

- For more information, see <http://www.nigms.nih.gov/Initiatives/PSI>
- (E) (NIGMS)

New Targets Identified for Intervention in the Development of Head and Neck Cancers: Over the last decade, cancer researchers have made significant progress in defining the molecular pathways involved in the development of head and neck squamous cell cancer. Studies that identify and characterize "key players" hold tremendous promise for the future treatment of these devastating cancers and ultimately improve the overall survival and quality-of-life for afflicted patients. One such key player is a family of proteins known as Wnt. Aberrant activation of the Wnt pathway has been found to be associated with cancer development and progression. Wnt promotes initiation of cancer by increasing the nuclear accumulation of β -catenin, an integral component of Wnt signaling, to activate target genes downstream. However, the mechanism of β -catenin recruitment to the Wnt target gene promoter largely is unknown. In an elegant study, the researchers discovered that β -catenin interacted with two other molecules (commonly called TBL1 and TBLR1), leading to the recruitment of β -catenin to the promoter of Wnt target genes. Decreasing TBL1 or TBLR1 via genetic knock-down did not affect the nuclear accumulation of β -catenin, but it did inhibit β -catenin significantly from binding to Wnt target gene promoter and the expression of Wnt target genes associated with tumor development. Moreover, depletion of TBL1 or TBLR1 inhibited invasive growth of tumor cells. These results provide fundamental knowledge about tumor genesis by revealing two new components required for nuclear β -catenin function. Targeting these molecules can have important therapeutic implications for head and neck cancer.

Technology Development

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- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDCR)

NIGMS/NCI Collaborative Access Team (GM/CA-CAT): Structural biology is a field in which scientists learn about molecules by determining their 3-D structures in atom-by-atom detail. Large user facilities called synchrotrons allow researchers to use X-rays to determine molecular structures more easily, quickly, and cheaply than ever before. Two NIH institutes (NIGMS and NCI) funded the development of a new experimental station at the Advanced Photon Source at Argonne National Laboratory. The new station includes three X-ray beamlines for use by scientists from across the United States to determine the detailed, three-dimensional structures of molecules. Two of these beamlines provide world-leading capabilities for X-ray diffraction data from very small protein crystals only a few microns in dimension. This research capability is important to understand basic biological processes and for drug design. The facility now is in full operation.

- For more information, see <http://www.gmca.anl.gov>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIGMS, NCI)

Scientists Accomplish Initial Catalogue of the Human Salivary Proteome: Secretions from the major salivary glands (parotid, submandibular, and sublingual) contain many peptides and proteins. They contribute to saliva's important roles in maintaining oral health, including antimicrobial, lubricating, buffering, and digestive properties. Salivary gland disorders, which result in severe dry mouth, compromise quality of life because they often lead to decay and periodontal diseases, mucosal infections, halitosis, taste impairment, and difficulties in swallowing and speaking. Saliva is a complex fluid; over the years, a number of salivary proteins have been reported but a systematic approach to catalogue all the proteins present in saliva was only initiated in 2004. NIH supported three teams of investigators to conduct the first comprehensive analysis of the salivary proteome. After samples were collected and analyzed, the data were standardized and integrated, yielding a salivary proteome that comprises 1,166 proteins. Of these proteins, 152 parotid and 139 submandibular/sublingual proteins were identified by all 3 research groups; these proteins form the core proteome. Most proteins identified were extracellular or secretory proteins, and involved in numerous molecular and cellular processes. A significant number of proteins represented in the salivary proteome also have been found to exist in the plasma or tear proteomes. This initial catalogue of the salivary proteome is a significant first step toward a comprehensive understanding of what the functions of saliva are, and how salivary composition is dependent on physiological variations, including on health and disease. This proteome could be the source of potential diagnostic and prognostic biomarkers for oral and systemic conditions.

- Denny P, et al. *J Proteome Res* 2008;7:1994-2006. PMID: 18361515.
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDCR)

Metabolic Network Model of a Human Oral Pathogen: The bacterium *Porphyromonas gingivalis* causes severe, chronic periodontal disease. Recently NIH-supported researchers constructed a complex metabolic network map for *P. gingivalis* with which to model the metabolic properties of all genomically identified components of the system. The scientists used a technique known as flux-balance analysis (FBA) to construct the model, which consisted of 679 metabolic reactions involving 564 metabolites. There was significant correlation between the model's predictions and the bacterium's experimentally observed metabolism. The true power of this model became apparent when "virtual knockouts" were employed to predict the effect of the loss of certain genes or metabolic pathways on growth rate, and the model very effectively predicted disturbances affecting biosynthesis of large molecules known as lipopolysaccharides. This is the first description of a model of this type for an oral periodontal pathogen. Still in their infancy, metabolic network models are a

logical extension of genome sequence data. They can provide the ability to perform virtual metabolic modeling of organisms with limited or no in vivo experimental histories. These models also could be applied to highly interdependent mixed microbial communities, including the oral microbiome, ultimately resulting in new biomedical applications. Such modeling greatly increases opportunities to discover new antibacterial drug targets. These studies provide new molecular targets for therapeutic drugs; they also can suggest the molecular mechanisms for virulence, intracellular persistence and survival, and ability of the bacteria to survive stresses from the (in this case, human) host defense mechanisms.

- Mazumdar V, et al. *J Bacteriol* 2009;191(1):74-90. PMID: 18931137. PMCID: PMC2612419.
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDCR)

New Biomaterials System Programs Cells in situ to Fight Cancer: In the body's immune response to foreign invaders, dendritic cells signal and activate other cells to initiate a generalized inflammatory response. Cell-based cancer vaccinations build on this natural tendency by isolating and activating a patient's dendritic cells using tumor antigens, and then injecting the reprogrammed cells back into the patient. The activated dendritic cells travel home to the lymph nodes and promote an antitumor response. Unfortunately, most transplanted dendritic cells die. Additionally, reprogrammed cells partially lose their effectiveness after injection back into the body. Thus, multiple rounds of injections are required to achieve significant effect. To address these limitations, investigators developed a multifunctional in situ dendritic cell reprogramming system composed of polymeric biomaterials that release cytokines to attract dendritic cells already within the lymph nodes into the biomaterials. The dendritic cells are then activated by the biomaterials. The biomaterials reduce their cytokine release at a controlled rate so that after activation, the dendritic cells will migrate away from the biomaterials back home to the lymph nodes and present tumor antigens to T cells found there. In a mouse model this sophisticated system provided protection from tumor development equal or superior to that provided by traditional cancer vaccines without the complications and costs of ex vivo cell manipulation and transplantation. The new system also provided much better control over the number of dendritic cells than traditionally generated cancer vaccines. This study demonstrates a powerful new application for polymeric biomaterials that could be used in the future against cancers and other diseases.

- Ali OA, et al. *Nature Materials* 2009;8(2):151-8. PMID: 19136947. PMCID: PMC2684978.
- This example also appears in Chapter 2: *Cancer*
- (E) (NIDCR)

Clinical Proteomic Technologies for Cancer: The Interagency Oncology Task Force (IOTF) held a workshop in October 2008, bringing together almost 60 participants representing NIH, FDA, industry, academia, and standards organizations. These key stakeholders in the proteomics community gathered to explore the regulatory requirements that will be needed to validate protein-based marker panels and any new technologies (hardware) for their intended use. Because there is a lack of guidance for multiplex proteomic assays, the workshop was an opportunity to engage CPTC scientists currently working through the issues that FDA will need to address when reviewing 510(k) submissions for proteomic technologies such as mass spectrometry and affinity arrays. FDA and the proteomic community posed relevant questions to each other with the goal of understanding the challenges and needs of each group. Outputs will include a publication on analytical validation issues that specific proteomic technologies should address when seeking FDA approval and mock 510(k) regulatory submissions for two technologies—mass spectrometry and affinity platforms. Together, these documents will help orient FDA to proteomic technologies in novel diagnostics and serve as a springboard for guidance to the proteomics community.

Technology Development

- For more information, see <http://proteomics.cancer.gov>
- For more information, see <http://www.cancer.gov/newscenter/pressrelease/FDAGuidance>
- (E/I) (NCI)

Unique Compounds Added to Chemical Libraries: Potent, drug-like molecules that selectively bind to the kappa opioid receptor have potential utility in the treatment of drug addiction, depression, psychosis and dementia, pain, and even HIV infection. Well more than 100 unique, new molecules constructed independently by two NIH-supported groups have been found to provide entirely new classes of kappa opioid binders. These molecules are potent and display a diversity of pharmacological activities that are under intensive active investigation.

- Beeler AB, et al. *J Comb Chem* 2005;7(5):673-81. PMID: 16153061.
- For more information, see http://www.cml.d.ku.edu/sbc_photos.shtml
- For more information, see <http://pdsp.med.unc.edu/indexR.html>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIGMS) (GPRA)

Transforming Health Care

Neural Interfaces Program: Neural interfaces are systems that operate at the intersection of the nervous system and an internal or external device, including neural prosthetics. Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. NIH pioneered the development of this technology, beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants, which help people with hearing impairments; respiratory and hand grasp devices for people with spinal cord injuries; and deep brain stimulation for Parkinson's disease, among other contributions. Current work aims to restore voluntary bowel and bladder control and standing to spinal cord-injured persons, allow paralyzed persons to control devices directly from their brains, improve cochlear implants, and improve deep brain stimulation, which may be applicable to many brain disorders. Through the years, the program has fostered the development of a robust research community, now including private sector companies, and represents a cooperative effort among several ICs, which also coordinate their efforts with programs that now are underway in the Department of Veterans Affairs and Department of Defense.

- For more information, see <http://www.ninds.nih.gov/funding/research/npp/index.htm>
- For more information, see <http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NINDS, NEI, NIBIB, NICHD, NIDCD)

Molecular Theranostics: New Technologies for the Diagnosis and Treatment of Diseases: The concept of combining a therapeutic with a diagnostic agent rapidly is evolving and goes beyond traditional diagnostic tests that screen or confirm the presence of a disease. With specialized molecular imaging techniques and biomarkers, theranostics might predict risks of disease, diagnose disease, and monitor therapeutic response leading to real-time, cost-effective treatment. NIH supports a number of teams that are developing novel theranostics and approaches that can be applied in clinical studies of human patients. A team of chemists and neurosurgeons at the University of Michigan is developing highly specific, dye-loaded nanoparticles capable of delivering targeted photosensitizers to improve the survival of brain tumor patients. This technique will allow neurosurgeons to visualize the brain tumors for surgical resection of the main tumor mass while eradicating remaining tumor cells through a process known as photodynamic therapy. These particles also contain imaging contrasting agents to visualize response to therapy.

- This example also appears in Chapter 2: *Cancer*
- (E) (NIBIB)

Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging: NIH supports 13 Roybal Centers whose objective is to improve the health, quality of life, and productivity of middle-aged and older people by facilitating translation of basic behavioral and social science to practical outcomes by developing new technologies and stimulating new "use-inspired" basic research in the behavioral and social sciences. Roybal investigators have made several key discoveries. For example: One Center has developed tools and technologies for identifying older adults at risk for automobile crash involvement, and is working with industry partners to develop and disseminate products based on these tools. Another Center has developed two evidence-based interventions from its in-depth work on physical activity for older adults. One program, Fit and Strong!, is targeted to older adults with lower extremity osteoarthritis, and one is targeted to older adults with developmental/intellectual disabilities (primarily Down syndrome). A Roybal investigator has developed instruments for self-efficacy appropriate for use with older adults with developmental/intellectual disabilities; these have been adopted internationally. Finally, a Center has developed a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Other companies have used this model to develop related products, and the model has spurred several new grant-funded research projects, including the development of a new medication tracker for older adults.

- For more information, see <http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/roybals.htm>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E) (NIA)

Smart Coatings for Implanted Biomaterials: A major limitation on the longevity of vascular grafts and implanted materials stems, not from failure of the graft or material itself, but typically, from the body's rejection in the form of blood clots or refusal to integrate with surrounding tissue. Recently, new classes of polymer-based biomimetics that resemble the cell surfaces of healthy blood vessels have demonstrated excellent resistance to platelet adhesion, a major problem for implanted materials in contact with blood. These biomimetic polymers have undergone successful preliminary clinical testing, and the same approach now is being used to develop biomimetic coatings resembling other types of human tissue. This technology recently was acquired by a major medical implant manufacturer.

- Kumar AM, et al. *J Am Chem Soc* 2008;130(4):1466-76. PMID: 18177047. PMCID: PMC2536642.
- Larsen CC, et al. *Biomaterials* 2007;28(24):3537-48. PMID: 17507089. PMCID: PMC2034336.
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIBIB)

Medical Technologies that Reduce Health Disparities: Appropriate medical technologies should be effective, affordable, culturally acceptable, and deliverable to those who need them. NIH is funding a research initiative to support the development of appropriate medical technologies for underserved settings. To ensure that the technology is appropriate, applications must involve interactions with underserved populations and/or collaborations with clinics in an underserved community.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-09-001.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NIBIB, NCMHD, NCRR, NIMH)

Research Training and Career Development

Research Training and Career Development

While the risk factors for heart failure—such as overweight, high blood pressure, and diabetes—have long been known, understanding its genetic origins is a much more recent pursuit and one of our most promising potential sources for novel drugs and therapies. Dr. Thomas Cappola was first drawn to this challenge during his medical residency when he began to study the molecular characteristics of the failing human heart. Over the next several years, NIH research training and career development awards helped provide him with the skills he would need to address such complex translational research questions. An opportunity to be a trainee on an institutional research training grant provided an in-depth exposure to patient-oriented research, and a clinical research curriculum award allowed his university to provide him with formal coursework in clinical investigation. Later support from the NIH loan repayment program permitted him to continue to pursue medical research without dwelling on the burden of repaying medical school loans, and an individual career development award provided protected time to further advance his research goals while working with a more senior investigator. This combination of NIH research training, loan repayment, and career development support has allowed Dr. Cappola to establish himself as an independent investigator pursuing his long-term research goal "to translate basic scientific discoveries into new approaches to treat and prevent heart failure," and in 2008, his use of genomic techniques to study heart failure was recognized with a Presidential Early Career Award for Scientists and Engineers.

Introduction

The biomedical and behavioral research conducted and supported by NIH—ranging from the very basic to the highly applied—has long been recognized as critical to advancing the quality of health care in the Nation and the world. As a result of NIH research, diseases such as AIDS, stroke, congestive heart failure, and diabetes increasingly are being treated or prevented more successfully. Further research undoubtedly will lead to new or improved medical therapies for a spectrum of diseases and disorders, but new advances in prevention, diagnosis, and treatment are dependent largely on the creativity, insight, and resources of the best scientists, and for these benefits to continue there must be a steady infusion of highly trained, well-equipped, and innovative new investigators. Research training is where cures begin.

Research training is where cures begin.

NIH research training and career development programs are designed to prepare new minds for research and ensure that diverse pools of highly trained scientists are available in sufficient numbers and with appropriate expertise to generate new discoveries, meet the needs of rapidly moving scientific field, and bring science to bear on complex and evolving health care challenges. By sponsoring research training and career development programs in universities, teaching hospitals, NIH laboratories, and other research-intensive settings, NIH expects that trainees and newly trained investigators not only will be exposed to the latest research findings and techniques, but also will be prepared to rise to the challenge of emerging problems in medicine and health. To further ensure that the research workforce will be poised to respond to evolving national and international public health needs, NIH takes steps to encourage individuals to focus on targeted or under-researched areas such as clinical and translational research, rare diseases, health disparities, and global health priorities.

The task of assessing and predicting research personnel needs across the entire spectrum—in the basic biomedical sciences, behavioral and social sciences, clinical sciences, oral health sciences, nursing research, and health services research—is daunting. Aligning the requisite expertise with public health needs is complicated by the evolving nature of biomedical, behavioral, and clinical research; the time required for research training; the international nature of research; and the mobility of the global research workforce. Preparing for a career in research generally requires a commitment of 8 to 10 years or more of predoctoral and postdoctoral training and career development; in the meantime, science is advancing, new diseases are emerging, and existing diseases are becoming better understood, diagnosed, and prevented.

In determining how best to sustain the continuing need for biomedical and behavioral scientists, NIH is guided by regularly scheduled analyses of the research workforce. Chief among these assessments are recurring studies conducted by the National Academies (NAS), which provide guidance on the fields in which researchers are likely to be required and on the number of new investigators needed in the basic biomedical, behavioral, and clinical sciences. NIH also routinely evaluates the outcomes of its training programs, comparing the subsequent research involvement of students and postdoctoral scholars who participate in NIH research training with their counterparts who were trained through other channels. Beyond such agency-wide assessments, individual ICs determine the need for new scientific personnel in mission-specific research areas through targeted evaluations, input from extramural investigators, and guidance from their national advisory councils.

NIH offers a broad range of research training and career development opportunities in its extramural and intramural research communities, through institutional training awards and individual fellowships, individual and institutional career development awards, continuing education, workshops, research grants, awards, and supplements to promote diversity or reentry into health-related research careers. Although its programs are largely directed toward graduate students and newly trained investigators, NIH offers a number of highly focused training and career development opportunities for individuals at other career stages, from college students to established scientists. NIH's research training and career development programs cover a broad range of basic biomedical, behavioral, and clinical research, including the interdisciplinary junctures between fields.

All NIH training and career development programs foster and encourage a diverse pool of participants. NIH expects that efforts to diversify the research workforce will lead to the recruitment of the most talented scientists from all groups, improved quality of the educational and training environment, more balanced and broader perspectives in setting research priorities, enhanced ability to recruit and retain subjects from diverse backgrounds into clinical research protocols, and improved capacity to address and eliminate health disparities. In addition to NIH's dedication to the inclusion of minorities and disadvantaged populations in the biomedical research workforce (also see the section on *Minority Health and Health Disparities* in Chapter 2), NIH is committed to the recruitment, retention, reentry, and advancement of women in biomedical research careers. Much progress has been made through the recent efforts of the NIH Director's Working Group on Women in Biomedical Careers. In response to recommendations from the Working Group and others, NIH extended the length of parental leave offered to NIH-sponsored trainees and fellows in 2008, and introduced the option for young scientists to pursue career development on a part-time basis in 2009.

NIH extended the length of parental leave offered to NIH-sponsored trainees and fellows in 2008 and introduced an option for part-time career development in 2009.

Catalogs of Research Training and Career Development Activities

In response to the mandate under SEC. 403 (a)(4)(C)(iv) of the Public Health Service Act to provide catalogs of research training activities, included here are live links to spreadsheets of:

- Funded Kirschstein-NRSA and National Library of Medicine *Institutional* Research Training Grants, FY 2008 and FY 2009
- Funded Kirschstein-NRSA and National Library of Medicine *Individual* Fellowship Awards, FY 2008 and FY 2009

Regarding postdoctoral scholars employed on research grants, NIH is implementing new reporting requirements. Grantees will be required to provide the names of all individuals associated with research projects for 1 or more months during the previous award year. In addition, individuals in postdoctoral roles will be required to establish and maintain personal profiles in the NIH eRA Commons. The Commons user ID for postdoctoral scholars will be reported in the list of individuals involved with NIH research projects. Information on postdoctoral scholars will be available for the next (FY 2010 and FY 2011) NIH Biennial Report.

Research Training and Career Development

Summary of NIH Activities

Extramural Programs and Progress: Research Training

Trans-NIH Programs and Initiatives

Training for a career in research typically requires a combination of specialized coursework and hands-on research experiences under the guidance of an established investigator. Most NIH-funded research training activities focus on predoctoral students and postdoctoral scholars and are provided either through training grants (T awards), which are awarded to institutions to support a coordinated program of training for a group of students or scholars, or fellowships (F awards), which directly support an individual's training. The principal NIH research training program for U.S. citizens and permanent residents, in size and breadth of coverage, is the Ruth L. Kirschstein National Research Service Award (NRSA) program. The goal of the NRSA program is to support promising students and postdoctoral scholars with the potential to become productive, independent investigators in fields relevant to NIH's mission. Training activities can be in basic biomedical or clinical sciences, in behavioral or social sciences, in health services research, or in any other discipline relevant to the NIH mission, and always include instruction in the responsible conduct of research. All ICs with funding authority award NRSA institutional research training grants and fellowships, except FIC and NLM. Reflecting the unique nature of their missions, the latter two ICs have distinct training authorities, separate from the NRSA program (see IC Programs and Initiatives below).

Through the NIH-wide program of NRSA institutional training grants and fellowships, NIH ICs supported nearly 16,400 graduate students and postdoctoral scholars at universities, teaching hospitals, and research centers in nearly every state in FY 2008. Institutional training grants form the core of NIH's research training programs, providing support to more than 80 percent of all NRSA program participants. Training grants play a particularly important role at the predoctoral level: approximately 60 percent of trainees are graduate students, often engaged in coursework and laboratory rotations in preparation for identifying an area of research for in-depth study. (See Appendix E for a breakdown on the demographics of NRSA participants and a summary of the number and type of doctoral degrees awarded to predoctoral NRSA recipients.)

Through the NIH-wide program of Ruth L. Kirschstein National Research Service Award institutional training grants and fellowships, NIH ICs supported nearly 16,400 graduate students and postdoctoral scholars at universities, teaching hospitals, and research centers in nearly every State in FY 2008.

Individuals interested in research training in universities or departments where there are no institutional training grants, as well as advanced students and postdoctoral scholars seeking tailored training opportunities, have the option of applying directly to NIH for an individual research training fellowship. NRSA fellowships provide recipients with valuable experience in initiating and testing their own research ideas before becoming full-fledged investigators.

Across NIH, NRSA training grants and fellowships help ensure the diversity of the research workforce by including features designed to provide research training opportunities to individuals from populations and backgrounds typically underrepresented in research (also see the section on *Minority Health and Health Disparities* in Chapter 2). Because part of the inherent challenge of recruiting talented individuals into research training programs is to have a pool of prepared applicants from which to draw, NIH offers undergraduate research training to honors students at selected institutions who have an explicit interest in a research career and intend to pursue postgraduate education leading to the Ph.D., M.D./Ph.D., or other combined degree. At the graduate and postdoctoral levels, NIH policy requires institutional training grant directors to take steps to recruit and retain trainees from underrepresented groups, including racial and ethnic groups and individuals with disabilities.⁵⁷ Through the Ruth L. Kirschstein NRSA Individual Predoctoral Fellowship (F31) to Promote Diversity in Health-Related Research, NIH also provides graduate students from underrepresented groups with opportunities to pursue research training through individual fellowship awards.

The relative diversity of research training participants reflects NIH's commitment to cultivating a broad-based scientific workforce. Among FY 2008 trainees and fellows who reported their race and ethnicity, 66 percent were white, 14.9 percent were Asian, 7.6 percent were African American, 7 percent were Hispanic, 1 percent were Native American, and 0.7 percent were Native Hawaiian or Pacific Islanders. More than 51 percent of trainees and fellows in FY 2008 were women.

NRSA training grants and fellowships may target broad-based or field-specific research training, depending on the needs identified by the administering IC. In recent years, this flexibility has allowed the NRSA program to respond to interest in greater integration of training activities across NIH to fulfill workforce needs shared by multiple ICs. The result has been a series of trans-NIH research training initiatives through the NIH Roadmap for Medical Research and other channels.

As the early Roadmap research training initiatives have matured, some have been selected for continuation and further expansion. The most notable of these are the Roadmap training grants and institutional career development awards in clinical and translational research that have been assimilated into Clinical and Translational Science Awards (CTSA). The CTSA program aims to accelerate the development of new treatments by transforming the way clinical and translational research are conducted. Creating multidisciplinary research teams that include physicians, basic scientists, statisticians, specially trained research nurses, informatics experts, and other specialists is central to this transformation. The CTSA program will grow through 2011 to serve about 60 academic sites, providing research training and career development opportunities in areas such as clinical research design, epidemiology, biostatistics, pharmacology, biomedical informatics, behavioral science, and ethics to more than 1,200 NRSA trainees and new investigators. (CTSA trainees are included in the NRSA data provided in Appendix E.)

In addition to its formal research training programs, NIH supports graduate and postdoctoral research experiences on research grants. Though not an NIH "program" per se, the impact of this support is significant. Graduate students and postdoctoral scholars acting as research assistants gain knowledge, skills, and experience that help prepare them for careers in research. To provide a better understanding of how many graduate students and postdoctorates contribute to research through roles as assistants, NIH investigators will be asked to identify all research project personnel beginning in FY 2010. At that time, all postdoctoral scholars also will be expected to have established accounts in the Electronic Research Administration (eRA) Commons, a Web-based system through which NIH administers grants and collects demographic and other information about its community of investigators. With the implementation of these changes, NIH will have much greater understanding of the overall biomedical research workforce supported by its funding.

To provide a better understanding of how many graduate students and postdoctoral fellows contribute to research in their roles as assistants, and to the overall workforce involved in NIH research, NIH investigators will be asked to identify all research project personnel beginning in FY 2010.

IC Programs and Initiatives

Because each NIH IC has its own particular research mission, individual ICs are responsible for determining how the workforce needs identified by NAS and others apply to their specific scientific fields, selecting individuals and institutions for NRSA or other research training awards to meet the needs identified, and reviewing annual progress toward building or enhancing capacity in the research workforce. Areas targeted for research training initiatives reflect the full array of NIH interests, from basic research training in biology and chemistry to clinical and translational research training in fields as distinct as cancer, infectious diseases, and aging. To ensure a supply of investigators attuned to the challenges of both research and patient care, a number of ICs also make awards for M.D./Ph.D. and other types of dual-degree training. The oldest and largest of these is the NIGMS Medical Scientist Training Program, which supports exceptional students pursuing an integrated program of graduate training in the biomedical sciences and clinical medicine.

Research Training and Career Development

While focusing on and supporting activities that address their respective missions and disease areas, ICs follow NIH-wide guidelines for NRSA research training and frequently collaborate to sponsor specific initiatives where there are overlapping interests or to stimulate interest in emerging fields. For example, eight ICs have partnered to support predoctoral training in biostatistics, through a program that integrates in-depth training in statistical theory and methodologies with basic biomedical, epidemiological, clinical, and behavioral research. In the area of neuroscience, multiple ICs support NRSA institutional training grants to provide broad neuroscience training for graduate students in the first and second years of study through the Jointly Sponsored Predoctoral Training Program in the Neuroscience. This program is affiliated with the NIH Blueprint for Neuroscience Research, a framework that brings together the 16 ICs and Offices that support neuroscience research and training, and provides a channel for coordinating their efforts. Other areas where ICs have come together to support research training on topics of joint interest include training at the interface of the behavioral and biomedical sciences, women's health, and bioethics.

NLM's research training portfolio generally parallels the structure and requirements of the NRSA program and reflects NLM's unique role as the primary Federal sponsor of biomedical informatics research and training. Like the ICs that provide NRSA research training, NLM prepares the next generation of informatics researchers and health information specialists through institutional grants (T15s), which support graduate and postdoctoral training in a broad range of topics, including health care information, bioinformatics, systems biology, imaging informatics, and public health informatics. NLM also offers a clinical informatics fellowship on the NIH campus designed to attract physicians and others to NIH to pursue research in clinical informatics. Unlike NRSA research training awards, some NLM training programs are open to master's degree holders seeking further graduate-level coursework and hands-on training. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.)

Reflecting the FIC mission to foster global health research and build research capacity in the developing world, FIC institutional training grants (D43s) differ from those offered by the NRSA program or by NLM by allowing a broader range of participants and emphasizing the development of institutional partnerships and collaborations between U.S. and international universities and scientists. Most FIC research training programs focus on providing research training to individuals from low- and middle-income nations, but a number of selected programs provide opportunities to U.S. students and postdoctoral scholars interested in international health research. FIC training programs are contributing to the building of sustainable research capacity in the developing world to enhance prevention, treatment, and control of infectious diseases, including HIV/AIDS, TB, and malaria, which are major causes of morbidity and mortality in those regions. Other FIC programs target research training in the areas of clinical, operational, and health services research; noncommunicable diseases; population studies; environmental and occupational health; trauma and injury; bioethics; and informatics training for global health. In order to foster long-term scientific partnerships between U.S. and foreign investigators and build research capacity, most FIC training grants require a joint collaboration between a U.S. and foreign institution.

Reflecting the FIC mission to foster global health research and build research capacity in the developing world, FIC institutional training grants emphasize the development of institutional partnerships and collaborations between U.S. and international universities and scientists.

Strength of Partnerships

Research training involves collaboration between NIH and its grantee institutions in the form of shared responsibilities and funding. In making NRSA training grant awards, for example, NIH relies on universities and other sites that receive support to select the best trainees, determine the curriculum and other aspects of the training program, and provide mentorship and supplemental funding to participating students and postdoctoral trainees. Although NRSA fellowships are targeted to individual students or postdoctoral scholars, NIH expects the sponsoring institutions to provide fellows with experienced mentors and supplemental research funding support. In some targeted NRSA research training programs, NIH also partners with other agencies, private foundations, and professional societies to achieve shared research training goals.

Partnerships between NIH and the private sector are helping to accelerate research training in creative ways. For example, NIH has partnered with the Howard Hughes Medical Institute to develop new graduate student training programs at the intersection of the biological and physical sciences and engineering. Through a distance-learning partnership, NIH has joined with Duke University School of Medicine to offer the Master of Health Sciences in Clinical Research degree to fellows and others on the NIH campus; to date, more than 65 individuals have completed the program. (Also see the section on *Clinical and Translational Research* in Chapter 3.)

NIH Training Program Evaluations and Assessments

Since the NRSA program was established in 1974, NIH training programs have been regularly reviewed and evaluated. NAS has undertaken regular reviews of the medical research workforce and made recommendations for modifications in the size and focus of the NRSA program. In addition, NRSA program processes and outcomes are regularly assessed through recurring program evaluations and annually measured against several Government Performance and Results Act (GPRA) goals. These reviews have been coordinated by OER, which oversees the NRSA program. Increasingly, however, individual ICs also are undertaking evaluations of their specific NRSA and other research training programs.

NAS Reviews. Over the past 30 years, the NRSA program has been the subject of more than a dozen studies by NAS, which has provided expert guidance on the fields in which researchers are likely to be required and on the number of new investigators needed in the basic biomedical, behavioral, and clinical sciences. The most recent NAS report on research training, published in 2005, noted that the NRSA program sets the standard for the entire research training establishment, attracting high-quality students into research and into fields of particular need.⁵⁸

The recurring nature of these NAS studies—the next will be issued in 2010—ensures that NIH research training programs reflect changes in science and research needs that inevitably occur over time. In recent years, NIH has followed recommendations from NAS committees for enhancing stipend levels, promoting the early completion of research training, and improving workforce data collection and analysis.

Evaluations of NRSA Training. Evaluations of the outcomes of NRSA research training routinely have found that graduate students participating in NRSA programs complete their degrees faster, are more likely to pursue research careers, and have greater subsequent success in research than do students not participating in NRSA programs.⁵⁹ Similarly, a 2006 evaluation of NRSA postdoctoral training found that NRSA postdoctoral fellows were more likely to successfully pursue research careers. More than 60 percent of former NRSA postdoctoral fellows who subsequently applied for a major NIH research grant received funding, compared to 36 percent of other postdoctoral fellows.⁶⁰

Government Performance and Results Act (GPRA) Goals. Every year, NIH assesses NRSA research training outcomes and program management against two goals established under GPRA. In the first of these goals, NIH seeks to measure the quality of its programs and ensure that substantial numbers of trainees and fellows are retained in research careers by comparing the proportion of former NRSA trainees and fellows who apply for and successfully receive NIH research grant support against their peers. Subsequent NIH support is one of several measures that reflect the impact of NRSA research training on participants' ability to successfully pursue and sustain a research career. To date, NIH has always met this GPRA goal, because NRSA trainees and fellows consistently outperform their counterparts.

The second training-related GPRA goal measures NIH progress in improving the efficiency of NRSA program management by developing and implementing the xTrain electronic system for appointing trainees to institutional training grants. Since its introduction in 2008, the number of universities using the xTrain system has tripled to more than 65, and in 2009 nearly 11 percent of training appointments were made electronically. Despite the substantial growth in institutions using xTrain, however, the number of appointments submitted electronically did not meet NIH's GPRA goal for FY 2009. As a result, NIH plans to begin requiring institutions to use xTrain to submit appointments to selected training grants in FY 2011, and continues to expect that the new system will be fully implemented by FY 2012, with 100 percent of trainees appointed to training grants electronically rather than through paper appointment forms. Ultimately, xTrain is expected to

Research Training and Career Development

save substantial staff time and eliminate data entry errors while increasing NIH's efficiency and enhancing the integrity of data used for program monitoring and evaluation purposes.

Institute and Center Training Evaluations. In addition to scheduled NIH-wide assessments of programs coordinated through OER, individual NIH ICs undertake periodic, targeted evaluations to improve implementation and assess outcomes of their own training programs. Institute-specific evaluations typically focus on research training needs in particular areas and often are conducted by independent “blue ribbon” panels of scientific leaders from around the country. For example, in 2008, NIMH convened a workgroup, composed of Advisory Council and outside experts, to evaluate its research training programs and make recommendations for future directions. Other recent and ongoing IC assessments include evaluations of the outcomes of the NIDDK research training fellowships and career development awards, CTSA training grants, and NIAMS research training programs. Details of these evaluations are provided in the Notable Examples below.

Extramural Programs and Progress: Career Development

Given the pace at which science advances, novel techniques and methods are introduced, and new fields emerge, investigators need opportunities to fully develop their scientific expertise and stay up to date. NIH Career Development Awards (K awards) address that need. Collectively, more than a dozen types of K awards support investigators as they establish their research careers, pursue new directions, or dedicate themselves to training and mentoring the next generation of scientists. Like the T and F training awards, some career development awards support institutional activities to nurture careers and others directly support individual development.

Many career development awards are designed for researchers at specific career stages, particularly newly trained investigators. The NIH-wide Pathway to Independence Award accelerates the transition from mentored to independent research by providing a bridging mechanism, through which an initial 1- to 2-year mentored period is followed by an independent phase, during which awardees establish their own research programs and apply for independent research support. Other “mentored” career development awards provide support for a sustained period of protected time for intensive research career development under the guidance of an experienced investigator. The expectation is that, with this experience, awardees will be able to take the final steps toward establishing independent research careers and becoming competitive for new research project grant funding. For example, NIH supports the Building Interdisciplinary Research Careers in Women's Health program, which pairs junior faculty with senior investigators in an interdisciplinary environment. At the other end of the career spectrum, a number of ICs provide Senior Scientist Research and Mentorship Awards. These awards provide salary support for outstanding senior scientists and recognized leaders so that, through an interval of protected time, they can focus intensively on their research and mentor new investigators.

The NIH-wide Pathway to Independence Award accelerates the transition from mentored to independent research by providing a bridging mechanism, through which an initial 1- to 2-year mentored period is followed by an independent phase, during which awardees establish their own research programs and apply for independent research support.

Several career development awards are particularly designed to foster the involvement of clinicians in research. The Mentored Clinical Scientist Research Career Development Award continues a long-standing NIH commitment to provide support and protected time to individuals with clinical doctoral degrees so that they can engage in an intensive, supervised research career development experience. The award supports both didactic study and mentored research for individuals with a wide variety of clinical degrees, including the M.D., D.D.S., D.V.M., and Pharm.D. A related program, the Mentored Patient-Oriented Research Career Development Award, supports the career development of clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research.

Other career development programs target specific areas of science. Examples include the Career Enhancement Award for Stem Cell Research, which enables investigators to acquire new research capabilities in the use of human or animal

embryonic, adult, or cord blood stem cells, and the Mentored Quantitative Research Career Development Award, which encourages investigators from quantitative science and engineering fields to focus on questions of health and disease.

Coordination and Oversight by the NIH Office of Extramural Research

Much as NIH collaborates with grantee institutions in conducting research training, OER also partners with ICs to coordinate and monitor awards for research training and career development across NIH. With active input from the ICs, OER establishes and implements policies and guidelines for each of the programs; determines broad national needs for basic biomedical, behavioral, and clinical research personnel; coordinates NIH-wide evaluations; develops trans-NIH research initiatives in which NIH ICs participate; and develops and maintains information systems to enhance program efficiencies. OER convenes monthly meetings of the NIH Training Advisory Committee to provide an agency-wide forum to identify and discuss issues related to research training and to provide opportunities to coordinate activities pertinent to the review, administration, management, and evaluation of training grants and fellowships.

Intramural Activities

The NIH intramural program provides opportunities for students, postdoctoral scholars, and clinicians to gain research experience within the more than 1,100 NIH intramural laboratories. A multifaceted array of programs provides a vibrant, scholarly environment and ensures strong research training experiences for future investigators and the continued professional development of intramural scientists.

Among the intramural program's offerings are summer internships for high school, college, and graduate students. Recent college graduates who plan to apply to graduate or professional school also can spend a year engaged in biomedical research working side by side with NIH scientists. Current graduate students can spend a summer, or even a year, as fellows engaged in biomedical research at NIH. The Graduate Partnerships Program (GPP) enables students to pursue research at NIH toward their degrees in partnership with a participating academic institution. By linking academic environments with the breadth and depth of research at NIH, the GPP creates a valuable graduate experience, one that purposefully focuses on skills of the future scientist and how discoveries will be made in the decades ahead. The Clinical Research Training Program (CRTP) is a yearlong program designed to attract the most creative, research-oriented medical and dental students to the NIH campus. CRTP fellows spend a year engaged in a mentored clinical or translational research project in an area that matches their personal interests and goals.

The Clinical Research Training Program is a yearlong program designed to attract the most creative, research-oriented medical and dental students to the NIH campus. Fellows spend a year engaged in a mentored clinical or translational research project in an area that matches their personal interests and goals.

Training opportunities continue when scholars gain their graduate degrees. Year-round, NIH intramural laboratories employ fellows from the United States and abroad, creating a thriving, multidisciplinary intramural research community. The Postdoctoral Intramural Research Training Award provides the opportunity for recent doctoral degree recipients, who are U.S. citizens or permanent residents, to enhance their research skills in the NIH intramural environment. Trainees pursue both basic and clinical research. A parallel program, Visiting Fellowships, serves foreign national doctoral-level scientists. For clinicians, there are opportunities for residency and subspecialty training, including graduate medical education (GME)-accredited programs (for program completion data, see Appendix E). These GME programs enable research-oriented clinicians to weave research experience and training into their post-medical school training.

In recent years, NIH's intramural program increasingly has focused on helping graduate students and postdoctoral fellows develop their career skills. To ensure that intramural trainees and fellows can successfully advance in their careers, NIH offers courses in scientific writing and grant writing, as well as presentation and teaching skills. In addition, intramural trainees and fellows—indeed, all members of the NIH community—benefit from access to a plethora of NIH courses, seminars, and science career resources. For example, every day across the NIH campus there are scientific seminars and

colloquia addressing the latest developments and discoveries in biomedical science; meetings of more than 100 Scientific Interest Groups that host forums and lecture series on cutting-edge issues of interest ranging from the Bioethics Interest Group to the Integrative Neural Immune Interest Group; and short- and long-term course offerings such as "Introduction to the Principles and Practice of Clinical Research" and "Principles of Clinical Pharmacology."

NIH Loan Repayment Programs

The NIH Loan Repayment Programs (LRPs) are a vital component of our Nation's efforts to attract eligible doctoral-level professionals to research careers in fields of special importance—clinical, pediatric, health disparities, contraception and infertility, and AIDS research. To encourage qualified scientists to pursue research in these critical areas, the LRP provides financial assistance for educational debt in exchange for a 2- or 3-year research commitment. Nearly 1,600 program participants each year receive up to \$35,000 annually in loan repayment and fulfill their commitments by conducting research in nonprofit, university, or government settings, or as an NIH employee.⁶¹ A 2009 evaluation⁶² of extramural LRP participants found that a substantial percentage remain in the research workforce after receiving a loan repayment award, and go on to receive subsequent research grants from NIH.

A 2009 evaluation of extramural Loan Repayment Program participants found that a substantial percentage remain in the research workforce after receiving a loan repayment award, and go on to receive subsequent research grants from NIH.

Conclusion

The initiatives and program reviews highlighted in the next section demonstrate NIH's ongoing commitment to building and maintaining a biomedical, behavioral, and clinical research workforce that can uncover new knowledge that will lead to better health for all Americans.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter of **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct
IC acronyms in **bold** face indicate lead IC(s).

Trans-NIH Research Training Programs

Ruth L. Kirschstein National Research Service Award (NRSA) Program: The Kirschstein-NRSA program is the primary route through which NIH provides research training to students and postdoctorates and ensures that a workforce of skilled investigators will be available to meet the Nation's needs in biomedical, behavioral, and clinical research. The program offers two modes of research training:

- NRSA Institutional Research Training Grants support predoctoral and postdoctoral research training programs at domestic institutions of higher education. Institutional research training grants allow universities, research institutes, and teaching hospitals to select specific trainees and develop a curriculum of study and research experiences tailored to provide high-quality research training. The training grant award provides stipends and offsets the cost of tuition for appointed trainees.

- NRSA Individual Fellowships provide support to promising students and postdoctoral researchers with the potential to become productive, independent investigators. Before applying, prospective fellows must identify a sponsor, who will help them develop into independent researchers. The individual fellowship award provides a stipend to the recipient, plus additional funds for tuition and an institutional allowance, which can be used for travel to scientific meetings.
 - For more information, see <http://grants.nih.gov/training/nrsa.htm>
 - For more information, see http://grants.nih.gov/training/T_Table.htm
 - For more information, see http://grants.nih.gov/training/F_files_nrsa.htm
 - (E) (**OER**)

Training M.D./Ph.D.s and Other Clinician Scientists: Investigators who are trained as both clinicians and scientists have long played a unique and vital role in health-related research. To ensure a continuing supply of these specially trained clinician investigators, NIH supports dual-degree training through dedicated NRSA awards, providing M.D./Ph.D. training through institutional Medical Scientist Training Program (MSTP) grants, and M.D./Ph.D. and other types of dual-degree training through individual predoctoral fellowship awards. More than 1,000 students per year receive dual-degree training through NRSA training grants and fellowships. By integrating clinical and research training, dual-degree programs allow participating students to launch their research careers much more quickly than would otherwise be the case.

- For more information, see <http://www.nigms.nih.gov/Training/InstPredoc/PredocOverview-MSTP.htm>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-09-232.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-09-232.html>
- (E) (**NIGMS, NHLBI, NIA, NIAAA, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIMH, NINDS, ODP/ODS**)

Training Activities of the Clinical and Translational Science Award Program: Clinical research requires unique skills in addition to those needed to care for patients, so academic health centers must equip members of clinical research teams with the special training and experience they need to succeed. NIH expanded its clinical research training programs through Roadmap T32 and K12 programs that largely have been assimilated into Clinical and Translational Science Awards (CTSAs). Clinical research trainees learn the skills needed to cultivate multidisciplinary research team collaborations and design research projects to compete successfully for funding in a mentored environment. The CTSA training program already is providing more than 1,000 research training and career development opportunities in multiple individual disciplines. As mandated in Section 106 of the National Institutes of Health Reform Act of 2006 (Pub. L. No. 109-482), NIH will evaluate the outcomes and effectiveness of the CTSA training programs. The evaluation will include surveys of trainees, scholars, and mentors and will address pediatric clinical research training issues. In addition, the evaluation will conduct secondary analyses of pediatric clinical research training data collected by the CTSA program. This is part of a much larger comprehensive evaluation of the CTSA program as a whole. Each individual CTSA recipient also evaluates his or her own training activities, and the CTSA Education/Career Development Key Function Committee provides a forum in which best educational practices can be identified. The CTSA program was initiated in September 2006, so the long-term impact of the CTSA program will not be known for 7 or more years. However, short-term process milestones and intermediate outcomes are expected in 1 to 7 years. For example, the CTSA consortium defined training standards for core competencies in clinical and translational research. The consortium identified the skills, attitudes, and knowledge that investigators need to participate successfully in multidisciplinary teams of clinician-scientists.

- For more information, see <http://nihroadmap.nih.gov/clinicalresearch/overview-training.asp>
- For more information, see <http://www.ctsaweb.org>
- For more information, see <http://www.ncrr.nih.gov>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NCRR**, Common Fund - all ICs participate)

Research Training and Career Development

NIH Roadmap Training for a New Interdisciplinary Research Workforce: As science has advanced over the past decade, it has become apparent that traditional organization of health research may, in some instances, slow the pace of scientific discovery. To foster changes in academic culture and interdisciplinary team approaches to research, in FY 2004, NIH announced several research training initiatives to provide interdisciplinary training to investigators at a range of career stages. One of these initiatives, the Interdisciplinary Health Research Training program, enabled institutions to develop postdoctoral training programs to provide newly minted scientists with interdisciplinary coursework and research training in fields outside their own, for example by integrating behavioral and/or social sciences with more traditional biomedical sciences research. A related program supported faculty interested in developing innovative and interdisciplinary courses, curricula, and education approaches. A final research training initiative, Training for a New Interdisciplinary Workforce, used a novel grant mechanism, the T90/R90, to support integrated interdisciplinary training at the undergraduate, graduate, and post-doctoral levels. Participants in this program all received training in at least two disciplines and had co-mentors from different fields. As Roadmap support for these programs nears an end, NIH announced in the summer of 2009 that the T90/R90 training and education award would be available for continued use by all NIH ICs.

- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp>
- (E) (NIDA, Common Fund - all ICs participate)

Blueprint Interdisciplinary Research Training: Under the auspices of the NIH Blueprint, interdisciplinary training programs have been established in computational neuroscience, neuroimaging, and translational research in the neurobiology of disease.

- The computational neuroscience programs seek to attract undergraduate and predoctoral students from the physical, mathematical, and engineering sciences to neuroscience research, and to expand the training of neuroscience students in quantitative sciences. Students learn how to develop models of neural systems or processes, test them experimentally, and then use experimental data to refine the models.
- The neuroimaging programs support predoctoral students and summer research intensives and provide comprehensive training in the breadth of imaging techniques and their application to neuroscientific questions. The goal of these programs is to train the next generation of neuroimaging researchers in the limitations, advantages, and underlying principles of currently available neuroimaging modalities.
- The translational research programs support students at multiple stages of their careers. The programs are designed to cross-train students in basic and clinical neuroscience, focusing not on specific diseases but on the biological mechanisms that are shared across diseases.

These Blueprint training programs are successfully seeding the field of neuroscience with highly qualified graduate students, postdoctoral fellows, and faculty.

- For more information, see http://neuroscienceblueprint.nih.gov/neuroscience_resources/training.htm
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E) (NIH Blueprint, NCCAM, NCCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

Intramural Training and Education: Working in collaboration with the NIH Fellows Committee, the Graduate Student Council, and IC training directors, the NIH Office of Intramural Training and Education has instituted several major annual events to serve trainees in the Intramural Research Program.

- The NIH Career Symposium provides an opportunity for NIH graduate students and postdoctoral trainees to learn about the various career opportunities available to them and to explore factors that lead to career success.

- The Graduate & Professional School Fair enables representatives of graduate and professional schools to recruit our college-age trainees. At the same time, workshops on writing personal statements, interviewing, and applying to positions are offered to the trainees.
- The International Opportunities Expo invites embassies, foreign funding agencies, and global corporations to recruit individuals interested in careers outside the United States.
- The NIH National Graduate Student Research Festival is a 2-day event held on the NIH campus to recruit the best graduate students to postdoctoral positions in the Intramural Research Program.

→ For more information, see <http://www.training.nih.gov/>

→ (I) (OIR)

The NIH Working Group on Women in Biomedical Careers: The Working Group was established as a trans-NIH committee by the NIH Director in response to the National Academies report *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, and to address the concerns of NIH intramural women scientists. The Working Group, co-chaired by the Director, NIH, and the Director, ORWH, is developing innovative strategies to promote the advancement of women in research careers at the NIH and throughout the extramural community. The Working Group has held two national meetings: the National Leadership Workshop on Mentoring Women in Biomedical Careers, and Women in Biomedical Research: Best Practices for Sustaining Career Success, the recommendations from which are being incorporated into new initiatives. An RFA, Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Research, which will bring new insights for enhancing the efficacy of career development and mentoring programs for women, was developed and 14 awards were funded. Through the efforts of the Working Group, NIH extended the parental leave period for intramural trainees and NRSA recipients to 8 weeks and helped establish the Mid-Atlantic HERC, an online listing of positions at member institutions that is searchable using two sets of criteria to assist dual career couples. The NIH tenure clock has been extended to accommodate family leave, and a mechanism has been developed to employ a temporary lab manager to continue lab operations during extended leave of an intramural investigator. The Working Group also is developing initiatives to promote bioengineering as a career choice for women.

→ For more information, see <http://womeninscience.nih.gov/>

→ For more information, see <http://www.midatlanticherc.org/>

→ (E/I) (ORWH, NCI, NCR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDCR, NIGMS, NINDS, NINR, NLM, OCPL, OD, OER, OIR)

Gauging the Role of Postdoctoral Researchers and Others in the Biomedical Workforce: To gain a better understanding of the size and characteristics of the biomedical research workforce, NIH is taking steps to identify all personnel involved in NIH research grants. Beginning with annual progress reports submitted in January 2010, NIH-funded investigators will be required to report on all personnel who have contributed a month or more of effort to their research projects, including postdoctoral researchers. In addition, postdoctoral researchers supported by research grants will be required to establish NIH Commons accounts, which will provide NIH with the ability to collect and report demographic information, such as gender, race, and ethnicity. These changes will provide a more complete picture of the research workforce supported by NIH and will enhance future evaluations of NIH training programs.

→ (E) (OER)

Extramural Loan Repayment Programs: Since they were established in FY 2000, NIH's extramural loan repayment programs have helped retain more than 4,500 new doctorates in research careers by repaying some or all of their educational debt. Most of the new applicants are early career researchers (within 6 years of terminal degree) with significant educational debt; in the most recent award cycle, median educational debt for new M.D. applicants was

Research Training and Career Development

\$146,978. An early evaluation of the programs recently confirmed that program participants—the majority of which are M.D.s and M.D./Ph.D.s—are more likely to remain in the NIH-funded research workforce and to receive subsequent research grants from NIH.

- For more information, see <http://www.lrp.nih.gov>
- (E) (**OER**)

International Bioethics Education and Career Development Award Program: Few developing country institutions provide formal education in research ethics, and there are only a small number of developed country programs for advanced research ethics education/training focus in depth on the internationally relevant aspects of research ethics. Therefore, few developing country scientists and health professionals conducting clinical or public health research have received extensive education and training in the principles of research ethics, international codes and legal aspects of ethical research, informed consent, elements of study design that affect the ethical conduct of research, and the ethical framework for provision of care and risk/benefit analysis for study participants. NIH's response to this was to develop a research bioethics training grant program that focuses on training ethicists who understand the fundamental principles and the cultural nuances of these principles as manifested in the guidelines being developed by other international organizations. Launched in March 2000, the International Bioethics Education and Career Development Award program is an institutional training grant that enables academic institutions to develop or expand current graduate curricula and training opportunities in international bioethics related to performing research in developing countries. Since 2001, more than 180 trainees from 40 developing countries have participated in the training programs.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-04-001.html>
- (E) (**FIC**, NCCAM, NHGRI, NHLBI, NIAID, NIDA, NIDCR, NIEHS, NIGMS)

NIH/FIC Clinical Research Training Scholars and Fellows Program: In response to a call from the President to invest in the economy by investing in global health research, as well as the growing interest in global health on U.S. graduate school campuses, FIC has expanded its Clinical Research Training Scholars and Fellows program, now in its fifth year, to provide early career mentored opportunities for U.S. postdoctorates and senior graduate students in the health sciences. The purpose of the program is to encourage the next generation of clinical research investigators to gain research experience working to address international health issues. The program provides new investigators with hands-on experience working in poor and transitional countries.

This program, which offers one year of mentored clinical research training at a site in the developing world, gives international opportunities to U.S. trainees, with the hope that such experiences during a formative period will encourage them to pursue careers in global health-related clinical research. The program, now expanded, provides support for clinical research training activities at the foreign sites, as well as a stipend for a foreign graduate student to be trained in tandem with the U.S. trainee during the clinical research year. Since the start of the program, the stipend amount has significantly increased to enable foreign site scholars to participate in the clinical research experience for a full year. In 2008, FIC expanded its commitment to the program and funded 33 U.S. scholars and 33 international scholars, 8 more U.S. and 9 more international scholars than the previous year.

- For more information, see http://www.fic.nih.gov/programs/training_grants/nih_fogarty.htm
- (E) (**FIC**, NCI, NCMHD, NIAID, NICHD, NIDA, NINR)

Framework Programs for Global Health—A Signature American Recovery and Reinvestment Act Project: In response to the growing interest in global health on U.S. college campuses and to further build the multidisciplinary teams and curriculum needed to address global health issues, NIH has used some of its American Recovery and Reinvestment

Act (ARRA) funding to enhance the Framework Programs for Global Health (FRAME). FRAME builds global health research capacity in the United States and in low- and middle-income countries by supporting the development of innovative, multidisciplinary global health programs. Through the FRAME program, institutions create administrative frameworks to network multiple schools (such as engineering, business, arts and sciences, law, communications, public health, medicine, environmental studies, and others) on one or more campuses to address global health issues and to develop multidisciplinary global health curricula for undergraduate, graduate, and professional school students. Each program leverages and enhances currently funded global health projects at the institution and encourages new training opportunities, collaborations, and research. Institutions may choose to partner with other institutions anywhere in the world to plan joint curricula, interactive programs, and even joint degrees. Specifically, ARRA funding will bolster Framework Programs for Global Health at Dartmouth University, Yale University, the University of California at Irvine, and the University of New Mexico.

- For more information, see http://www.fic.nih.gov/programs/training_grants/framework/index.htm
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-08-001.html#Section1>
- For more information, see <http://www.nih.gov/news/health/may2009/fic-12.htm>
- (E) (FIC, NCI, NIBIB, NICHD, NINDS) (ARRA)

IC-Specific Programs and Initiatives

Predoctoral Research Training in Biostatistics: A workforce of biostatisticians with a deep understanding of statistical theory and new methodologies is vital to meet the biomedical, clinical, and behavioral research needs of the United States. With that end in mind, NIH has funded 13 predoctoral training programs in biostatistics to support 47 predoctoral trainees. The training program integrates biostatistical theory and evolving methodologies with basic biomedical research, including bioinformatics, genetics, molecular biology, cellular processes, and physiology, as well as epidemiological, clinical, and behavioral studies.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/par-04-132.html>
- (E) (NIGMS, NCI, NHGRI, NHLBI, NIAID, NIDCD, NIDCR, NINDS)

Training for Cancer Research: The Center for Cancer Training is preparing a workforce to advance cancer research through a scientifically integrated approach. The Center coordinates intramural and extramural research training, career development, and educational opportunities. The Interagency Oncology Task Force Joint Fellowship Program, an NIH-FDA partnership, supports development of new medical products by training scientists in research-related regulatory review. The Cancer Education and Career Development (R25T) Program supports career development for early career investigators transdisciplinary sciences, producing a generation of researchers cross-trained in disparity research areas and poised to conduct team research. The Calabresi Award in Clinical Oncology (K12) Program brings together clinicians and basic scientists to design and implement hypothesis-based therapeutic trials, promoting translation research findings from bench to bedside. The Howard Temin Pathway to Independence Award in Cancer Research (K99/R00) assists early career basic scientists in transitioning from mentorship to independent research by providing funding to complete their fellowships, support their first investigator-initiated research programs, and launch their research careers. The Comparative Molecular Pathology Unit (CMPU) trains translational research investigators by incorporating interdisciplinary education in veterinary medicine with training in human biomedical research. Research Supplements to Promote Diversity in Health-Related Research create the foundation to attract and prepare qualified individuals from underrepresented and underserved populations and individuals with disabilities for careers in cancer research.

- For more information, see <http://www.cancer.gov/cct>
- For more information, see http://ccr.nci.nih.gov/resources/molecular_pathology/training.asp

Research Training and Career Development

- This example also appears in Chapter 2: *Cancer*
- (E/I) (NCI)

Predocutorial Training at the Interface of the Behavioral and Biomedical Sciences: The NIH Institutional Training Grant Program, "Training at the Interface of the Behavioral and Biomedical Sciences," provides an interdisciplinary research training experience and curriculum for predoctoral trainees that integrate both behavioral and biomedical perspectives, approaches, and methodologies. Through coursework, laboratory rotations, and programmatic activities that reinforce training at this interface, the program aims to develop basic behavioral scientists with rigorous training in the biomedical sciences, who are available to assume leadership roles related to the Nation's biomedical, behavioral, and clinical research needs.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-06-503.html>
- For more information, see <http://www.nigms.nih.gov/News/Results/BehavioralBiomedical070207.htm>
- (E) (NIGMS, NCI, NHGRI, NHLBI, NIAID, NIDCD, NIDCR, NINDS)

Informatics Research Training Programs: Exploiting the potential of information technology to augment health care, biomedical research, and education requires investigators who understand biomedicine as well as knowledge representation and decision support. NLM is the principal source of extramural funding for research training in the fields of biomedical informatics, supporting approximately 270 trainees at 18 institutional training programs throughout the country. NLM also provides intramural informatics research training opportunities for another 70 students, postdoctorates, and visiting scientists, as well as training and career development fellowships for health science librarians on the NIH campus and at academic health sciences centers across the country. Collectively, NLM's research training programs encompass health care informatics, bioinformatics, clinical research translational informatics, and public health informatics. Recent highlights and developments in informatics training include:

- A congressional supplemental appropriation for FY 2008 allowed NIH to add 26 NLM training slots.
- A Diversity Short-Term Trainee Program was implemented to improve the diversity of informatics trainees, with funding for 18 trainees at 7 training programs.
- Funds from the American Reinvestment and Recovery Act were committed to support an additional 56 2-year slots at 10 of its informatics training programs.
- A new Clinical Informatics Postdoctoral Fellowship was established to attract young physicians to NIH to pursue research in informatics.

- For more information, see <http://www.nlm.nih.gov/training.html>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (NLM) (ARRA)

AIDS International Training and Research Program: The AIDS International Training and Research Program (AITRP) began in 1988 as one of the first of a new generation of research training programs sponsored by FIC. This program supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries (LMICs) to conduct multidisciplinary biomedical and behavioral research to address the AIDS epidemic in their countries. This program provides training for scientists from LMIC institutions to strengthen HIV-related research and public health capacities at their institutions. AITRP has trained more than 1,500 trainees. Importantly, several partnerships between AITRP programs and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) were developed in 2008 and 2009. The training provided under the AITRP program targets a cohort of scientists who benefit from the critical thinking and problem-solving skills received through research training. These skills move them forward in their careers into leadership and policymaking positions in public health in their countries. Many PEPFAR programs are directed in-

country by clinician/scientists who have received FIC-supported training. This training, therefore, is an important foundation for the long-term sustainability of the PEPFAR programs. There are many successful partnerships between PEPFAR country teams and FIC AITRP grantees in Zambia, Tanzania, and Cote d'Ivoire.

- For more information, see http://www.fic.nih.gov/programs/training_grants/aitrp/
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (FIC, NCI, NHLBI, NIAID, NICHD, NIDA, NIMH, OD)

Research Training and Career Development for Veterinarians in Translational Biomedical Research: Two recent reports from the National Academies, *National Need and Priorities for Veterinarians in Biomedical Research* and *Critical Needs for Research in Veterinary Science*, have confirmed the shortage of veterinarians involved in biomedical research. To address the shortage, NIH provides research training awards ("T" Awards) in biomedical research specifically for veterinarians and veterinary students. During FY 2008, more than 75 veterinarians received research training under the "T" mechanism. The mentored Career Development Awards ("K" Awards) to veterinarians serve as a bridge for postdoctoral fellows to become independent investigators. In FY 2008, 22 career development "K" awards were made to young veterinary investigators to increase the number of biomedical researchers with this expertise. Additionally, another initiative encourages the training of veterinarians in nonhuman primate clinical medicine at NIH-supported primate centers to address the shortage of clinical veterinary support for research primate colonies.

- For more information, see http://www.ncrr.nih.gov/career_development_opportunities/individual_training_grants/
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NCRR)

Summer Institutes to Train Behavioral, Social and Biomedical Researchers: In addition to its formal research training and career development programs, NIH provides special opportunities for students and investigators to gain hands-on experience in research methodologies particularly relevant to behavioral and social science fields.

- Since 2000, NIH has sponsored the Summer Institute on Design and Conduct of Randomized Clinical Trials (RCTs) Involving Behavioral Interventions. Each year more than 200 applicants compete for 35 fellowships to participate in the 2-week course. Leading researchers and statisticians provide grounding in the principles underlying objective clinical trials; challenges posed by behavioral RCTs; alternative RCT designs; appropriate strategies for enrollment, randomization, and retention of participants; methods for monitoring, coordinating, and conducting RCTs; and strategies for appropriate statistical analyses of RCT data.
- In 2009, NIH initiated an annual Institute on Systems Science and Health, to encourage investigators to make use of modeling and related methodologies to tackle complex problems in behavior and health. The 46 participants in the week-long institute gained a broad overview of systems science methodologies and hands-on training in one of three systems science methodologies (agent-based modeling, system dynamics modeling, or network analysis).

- For more information, see <http://www.chronicdisease.org/i4a/pages/index.cfm?pageid=3851>
- For more information, see http://obssr.od.nih.gov/training_and_education/annual_Health_Services_Research_on_social_work/hsr.aspx
- For more information, see http://obssr.od.nih.gov/training_and_education/annual_Randomized_Clinical_Trials_course/RCT_info.aspx
- (O) (OBSSR, CDC)

Research Training and Career Development

Web-Based Learning Modules for Behavioral and Social Sciences Research: NIH is developing Web-based learning modules to enhance the conduct of behavioral and social sciences (BSS) research related to health. These courses provide interactive learning environments for behavioral, social, and biomedical scientists with the goal of facilitating team-based, multidisciplinary research.

- *Behavioral and Social Sciences Research Interactive Textbook.* NIH is supporting the development of an interactive, online course on research methods and tools for researchers engaging in BSS research on health-related topics. The project aims to demonstrate the potential of BSS research to enhance biomedical research, serve as a resource center for the most current and high-quality BSS research methods, reveal how to obtain authoritative answers to methodological questions easily and efficiently, and identify consistent and rigorous quality standards for the research community.
- *Evidence-Based Behavioral Practice.* Another project established a website and three training modules. A goal of the project is to develop online learning tools to help behavioral practitioners and students integrate research and practice in real-world conditions.
- *Genetics Educational Materials for Behavioral and Social Scientists:* An NIH-supported coalition is creating a Web-based educational program in genetics/genomics for the BSS research community. The program will help train scientists capable of working in interdisciplinary teams to improve our understanding of how interactions among genes, behaviors, and environments contribute to health and disease.

→ For more information, see <http://www.ebbp.org/>

→ (E, O) (**OBSSR**)

NINR Intramural Training Initiatives: Through a range of initiatives, NINR's intramural program bolsters the Institute's formal extramural research training programs and expedites the development of productive nurse scientists, many of whom also will serve as nursing faculty.

- The Summer Genetics Institute (SGI) is an intense, 2-month, full-time summer research training program for faculty, graduate students, and advanced practice nurses that has been supported annually by NIH since 2000. Hosted by the NINR Division of Intramural Research, the SGI features classroom and laboratory components that are designed to provide a foundation in molecular genetics for use in clinical practice and the research laboratory.
- For recently graduated, doctorally prepared nurse scientists, NIH sponsors the K22 Career Transition Awards, which are designed to facilitate the transition of postdoctoral trainees to independent research careers. Awardees receive up to 3 years of postdoctoral research training in intramural laboratories in Bethesda, Maryland, followed by 2 years of extramural support as they begin tenure-track faculty positions.
- Through its participation in the NIH Graduate Partnerships Program, NINR partners with schools of nursing to provide doctoral students with opportunities for up to 2 years of research training at the NIH. Participating students conduct research under the guidance of an NIH intramural investigator, in areas such as symptom management, genetics, or end-of-life/palliative care.
- Finally, in 2009, NINR and the NIH CC, in association with the Bravewell Collaborative, began offering a 2-year fellowship for research in integrative medicine. The fellowship combines research experiences in the NIH intramural laboratories with instruction through the University of Arizona's Program in Integrative Medicine.

→ For more information, see <http://www.ninr.nih.gov/Training/TrainingOpportunitiesIntramural/>

→ (I) (**NINR**)

Informatics Training for Global Health: As biomedical information has increased exponentially in recent years, computer-based tools have been developed to access and analyze this information and to aid the process of research design, data management, and data analysis. The sheer volume of data generated in many biomedical and behavioral research projects and in clinical trials can no longer be managed effectively without electronic help. Further, access to computers and the Internet is becoming commonplace in research institutions throughout the developing world. To take

advantage of these tools, individuals with the advanced skills to use them are critically needed. However, despite the central role informatics plays in global health, many low and middle income country (LMIC) institutions have very few informatics experts and a very weak information technology infrastructure. There is a critical need to train local experts who are able to develop local research applications or modify existing platforms to provide tools that are appropriate for the needs, culture, and infrastructure of their institutions and countries. In response, NIH's Informatics Training for Global Health program aims to develop human capital to meet global health challenges, to support the development of research hubs in LMICs, and to bolster the development of expertise in the use of information and communication technologies in support of research and research training.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-09-001.html>
- This example also appears in Chapter 3: *Technology Development*
- (E) (FIC, NHGRI, NIBIB, NLM)

Strength from Partnerships

Interdisciplinary Graduate Research Training: A Public-Private Partnership Between NIH and HHMI: Howard Hughes Medical Institute (HHMI) and NIH have developed a joint initiative for Interdisciplinary Graduate Research Training. This innovative public-private partnership, begun in 2005, is intended to facilitate the development of graduate student training in emerging interdisciplinary research environments and to increase the number of interdisciplinary researchers working at the intersection of the biological and physical sciences and/or engineering. Funding for Phase 1 of the initiative was provided by HHMI, which awarded \$10 million in 3-year grants to 10 institutions to pilot new and innovative ways to train interdisciplinary scientists. The second phase of this initiative, recently funded by NIH, provides support for graduate student training in interdisciplinary research. The training environments link the educational and research training missions of multiple schools and departments, including biology, chemistry, computational mathematics, engineering, materials science, and physics. They also have many innovative didactic and community-building activities, including "boot camps," team challenges, interdisciplinary courses and laboratories, courses on communication and collaboration, team mentoring, and interdisciplinary rotations, retreats, and seminars.

- For more information, see <http://www.hhmi.org/news/112205.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-08-003.html>
- (E) (NIBIB)

Clinical Research Training and Medical Education at the NIH CC: NIH develops, administers, and evaluates clinical research training and medical education initiatives that contribute to the professional growth of the clinical and translational research community, including medical and dental students, physicians in residency and fellowship training programs, established investigators, allied health professionals, and laypersons. The clinical research curriculum is offered at NIH and domestic and international locations. The curriculum consists of the "Introduction to the Principles & Practices of Clinical Research," "Principles of Clinical Pharmacology," and "Ethical & Regulatory Aspects of Clinical Research" courses as well as on-line courses for principal investigators. Extramural researchers have a new opportunity to access the rich training experiences available on the NIH campus via a "Clinical Research Management Sabbatical," which allows clinical investigators to come to the NIH CC to develop the leadership skills needed to create or enhance an optimal environment for conducting clinical research. The NIH CC also has partnered with extramural collaborators and industry to enrich its educational offerings. Via videoconferencing, Duke University School of Medicine offers NIH physicians and dentists an opportunity to receive a Master of Health Sciences in Clinical Research. The Clinical Research Training Program, a partnership supported by NIH and a grant to the Foundation for NIH from Pfizer Inc., trains 30 advanced medical and dental students annually in clinical or translational research.

Research Training and Career Development

- For more information, see <http://www.cc.nih.gov/training/index.html>
- (I) (CC)

Paul B. Beeson Career Development Awards in Aging Research: The Beeson Awards, co-supported by NIH, the American Federation for Aging Research, and several other philanthropic concerns, offer 3- to 5-year faculty development awards to outstanding junior and mid-career faculty committed to academic careers in aging-related research, training, and practice. Beeson scholars receive funding and resources to pursue their innovative research; protected time for research; mentorship through their own institutions and through the program itself; and extensive networking opportunities. Since their inception in 1995, the Beeson award has provided nearly \$80 million to 152 independent investigators, many of whom have gone on to become leaders in the field of aging research.

- For more information, see <http://www.beeson.org>
- (E) (NIA)

NIH Training Program Evaluations and Assessments

Annual Assessments of Research Training: Every year, NIH monitors the effectiveness of its research training programs by analyzing the extent to which former Kirschstein-NRSA trainees and fellows remain engaged in biomedical research. Results of these annual assessments routinely have indicated that Kirschstein-NRSA postdoctoral trainees and fellows are more likely to remain active in biomedical research than their peers in the same fields, as indicated by the greater percentage applying for and receiving NIH research support within 10 years of their training.

- For more information, see <http://nihperformance.nih.gov/NR/rdonlyres/9A12CAF4-C39A-4D29-96A4-A57863A6B3A7/12537/FY10OnlinePerformanceAppendixNIHFINAL.pdf>
- (O) (OER) (GPRA)

Career Development for Physician-Scientists: NIH supports a number of institutional career development programs for physician-scientists at leading medical institutions across the country. Some of these programs are open to physicians of any specialty, while others are targeted specifically to physicians with particular specialties, such as pediatrics, medical rehabilitation, obstetrics-gynecology, or critical care medicine. NIH has tracked the career progress of physician-scientists who have participated in several of these programs. The results indicated that, depending on the specific program, between 60 and 85 percent of participants subsequently applied for an NIH grant, and between 50 and 75 percent of participants became a principal investigator on an NIH grant. Program participants received funding from all 24 award-granting ICs at NIH. The success rate for subsequent funding varied by the specific program, institution, sex, time since degree, and medical subspecialty. The findings will be used to refine program objectives and to target specific areas for improvement.

- (O) (NICHD)

xTrain: As part of its commitment to electronic research administration, NIH has introduced a system to allow information on participants in institutional research training grants and career development awards to be transmitted to NIH electronically. Through this new system—xTrain, program directors electronically can appoint students and postdoctorates to research training and career development awards and report to NIH when their training is complete. Ultimately, xTrain will replace the paper appointment forms that have been used by NIH training programs since the 1970s and will help NIH manage its research training and career development activities more effectively. Since the introduction of xTrain in June 2008, more than 65 universities have begun using the system. By 2012, all appointments to NIH training grants and institutional career development awards are expected to be made via xTrain.

- For more information, see http://era.nih.gov/services_for_applicants/other/xTrain.cfm
- (E) (OER) (GPRA)

Evaluation of Extramural Research Training and Career Development Programs at NIAMS: NIAMS conducted an outcome evaluation to assess the success of postdoctoral research trainees who received NIAMS grants and awards through its extramural research training and career development awards program. Like other NIH training and career development grants and awards programs, the NIAMS program is intended to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to biomedical and behavioral research. NIAMS's overall objective is to use a combination of institutional training grants and individual fellowships to ensure a continuing supply of well-trained scientists, prepared to conduct cutting-edge research related to musculoskeletal, skin, and rheumatic diseases. The specific grants and awards that were evaluated are the National Research Service Award (NRSA) institutional training grant (T32), NRSA individual research training grant (F32), and Mentored Career Development Awards (K01 and K08). While NIAMS uses other grant and award mechanisms, these awards were selected both because they represent a high proportion of the total dollars awarded, and because there is sufficient information available about recipients to assess their career progress over time. Overall, a working group of outside experts considered these programs to be successful in maintaining a highly trained workforce, and provided 10 recommendations for consideration. NIAMS has established an internal working group to review each of the recommendations carefully, and several key changes to the program already have been implemented.

- For more information, see http://www.niams.nih.gov/News_and_Events/Meetings_and_Events/Reports/2007/training_grant_eval_final_report.asp
- (E) (NIAMS)

Investing in the Future: 2008 National Advisory Mental Health Council Workgroup on Research Training: The National Advisory Mental Health Council convened a workgroup, composed of both council members and outside experts, to develop a framework outlining NIMH's research training priorities. The workgroup's goal was to identify the steps needed to develop a workforce equipped with the cutting-edge knowledge, skills, and perspectives that will accelerate the field of mental health research. The training report summarizes important characteristics of the future NIMH research workforce and considers three key issues: the diversity of the workforce; international students and postdoctoral scholars; and researchers holding dual M.D./Ph.D. degrees. The report includes recommendations for the future direction of NIMH-supported research training programs and initiatives, as well as those for program assessment and dissemination to the extramural research community. The report's recommendations were made with the hope that by developing an even stronger mental health research workforce, NIMH will increase the rate of innovative discoveries, and ultimately lead to improved treatment and functioning for people living with mental illness.

- For more information, see <http://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/investing-in-the-future.pdf>
- (E) (NIMH)

Review of the International Clinical, Operational, and Health Services Research and Training Award (ICOHRTA): NIH reviewed the first 5 years of the ICOHRTA program. The purpose of the review was to analyze program implementation, identify near-term outputs, and make recommendations for future improvements to the program. Overall, the panel concluded that the program was successful and productive in its first 5 years. Notable accomplishments highlighting the effectiveness of the training program include the following:

Research Training and Career Development

- A total of 129 trainees from 18 low- and middle-income countries in 5 world regions have been associated with the program for at least 6 months, and many more individuals have participated in shorter-term training activities.
- Five former ICOHRTA trainees have competed successfully for NIH R01 awards, and one additional trainee is principal investigator on a Cooperative Agreement with the Centers for Disease Control and Prevention. Former trainees also collaborate on at least three NIH awards made to U.S. principal investigators since 2001, including an FIC Trauma award and a Fogerty International Research Collaboration Award.
- A total of 381 peer-reviewed journal articles are known to have been associated with ICOHRTA awards, as are an additional 47 nonpeer reviewed publications such as book chapters, books, and policy documents.
- ICOHRTA played a key role in several important national public health and policy projects.

→ For more information, see http://www.fic.nih.gov/programs/training_grants/icohрта/

→ (E) (FIC, NCCAM, NIA, NIDA, NIDCR, NIMH)

Evaluation of NIDDK Research Training Programs: Each year, NIDDK evaluates the 5-, 10-, and 15-year outcomes of individuals who received either Career Development Awards (K awards) or Individual Postdoctoral National Research Service Awards (F32 awards). The most recent evaluation, conducted in 2008, included outcome data from individuals whose grants ended in 1993, 1998, and 2003. A total of 180 former F32 fellows and 139 former K awardees were included in the evaluation. The data showed that 45 to 58 percent (ranges reflect the high and low values of the groups evaluated) of the F32 postdoctoral fellows remained in research at the time of the evaluation. In addition, 50 to 60 percent of the fellows had applied for additional NIH funding; of those who applied, 55 to 68 percent were successful. Among K awardees, 62 to 85 percent remained in research at the time of the evaluation. Furthermore, 71 to 85 percent of the K awardees had applied for further NIH funding, and 75 to 81 percent of those who applied were successful. Data on current funding status and on the number of publications during the last year—and the subsequent 2 years—of the F32 or K award funding also were collected, along with the current position of each awardee, when available. Overall, NIDDK concluded that the trainees have been successful with respect to scientific progress, continuation in research, and applying for funding. NIDDK uses these data to guide its research training programs, which aim to advance research progress through the training of investigators in research relevant to diseases within the Institute's mission. NIDDK also has discussed results of training program evaluations with its Advisory Council for additional input.

→ (O) (NIDDK)

Trans-NIH Extramural Career Development Programs

Research Career Development Programs: One of the most challenging transitions in any research career is the progression from postdoctoral trainee to independent scientist. NIH has long used the Research Scientist Development Award (K01) to foster the successful transition of individuals who hold a research or health-professional doctoral degree or equivalent. To support the transition of junior-level clinically-trained investigators, NIH also offers the Mentored Clinical Scientist Development Award (K08) and the Mentored Patient-Oriented Research Career Development Award (K23). For postdoctoral fellows seeking to transition to faculty positions, awards such as the Career Transition Award (K22) and the Pathway to Independence Program (K99/R00) provide mentoring, protected time, and financial support to ease the transition to faculty positions. At the institutional level, NIH offers several Mentored Clinical Scientist Development Awards (K12) that provide support to newly trained clinicians at an institution who are developing their independent research skills and experience. Other specific career development awards are tailored to meet the needs of different research areas and recipients at different career levels.

→ For more information, see <http://grants.nih.gov/training/careerdevelopmentawards.htm>

→ For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-09-040.html>

→ For more information, see <http://grants2.nih.gov/grants/guide/pa-files/PA-09-042.html>

→ For more information, see <http://grants2.nih.gov/grants/guide/pa-files/PA-09-043.html>

- For more information, see <http://grants2.nih.gov/grants/guide/pa-files/PA-09-036.html>
- (E) (**OER**)

Building Interdisciplinary Research Careers in Women's Health (BIRCWH): The Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program is an interdisciplinary, mentored, career development initiative that supports junior faculty men and women who are conducting research in women's health. Each scholar has at least two mentors from different disciplines that are part of their interdisciplinary mentoring team. The BIRCWH is co-funded by the NIH Office of the NIH Director, several NIH ICs, and the Agency for Healthcare Research and Quality (AHRQ). To date, 50 BIRCWH programs have been established at 38 institutions and there are currently 26 active BIRCWH sites. More than 378 scholars have participated, of which 79 percent are women. Scholars have published more than 1,300 publications and have successfully competed for 282 NIH research grants. BIRCWH plays a critical role in maintaining the pipeline of junior faculty who are available to conduct women's health research.

- For more information, see <http://orwh.od.nih.gov/interdisciplinary/bircwhmenu.html>
- (E) (**ORWH**, AHRQ, NCI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIEHS, NIMH, ODP/ODS)

Disparities Research and Education Advancing Mission Career Transition Award: This award program facilitates the transition of early-stage investigators working in health disparities or areas that address health disparity conditions and populations from the mentored stage of career development to the independent stage of investigator-initiated health disparities research. The program provides an opportunity for investigators to develop solid research skills during the initial period of up to two years of study and research within the NIH Intramural Research Program. The award may also include a follow-on period of up to three years of salary and mentored research support at the candidate's current institution or organization or an academic or research grantee institution of the candidate's choice. This period of extramural support will facilitate the transition to independence as a researcher in health disparities research.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-10-001.html>
- (E) (**NCMHD**)

Research Training and Career Development

⁵⁷ Consistent with Section 487(a)(4) of the PHS Act.

⁵⁸ For more information, see http://www.nap.edu/catalog.php?record_id=11275#toc.

⁵⁹ For more information, see http://grants.nih.gov/training/career_progress/index.htm.

⁶⁰ For more information, see http://grants1.nih.gov/training/NRSA_report_5_16_06-2.doc.

⁶¹ For more information, see http://www.lrp.nih.gov/reports_and_statistics/index.aspx

⁶² For more information, see http://www.lrp.nih.gov/pdf/LRP_Evaluation_Report_508final06082009.pdf

Health Communication and Information Campaigns and Clearinghouses

Health Communication and Information Campaigns and Clearinghouses

Norma knew she had some of the risk factors for heart disease—high cholesterol, age, and a family history. But it wasn't in her plan to sit around and wait for the worst. "I've had a lot of friends who have had heart attacks, and this has made me aware that I need to take care of myself. You can't wait until a heart attack happens, by then it's too late." So Norma and many other women are grabbing life by the reins and doing what they can to prevent heart disease through a good diet, physical activity, and talking to their doctor about risks and warning signs.

"I try to live a healthy lifestyle by eating healthy foods and finding creative ways to exercise—like dancing," says Norma, who has been touched personally by NIH's Heart Truth®⁶³ public information campaign. The Heart Truth® message is paired with an arresting visual—the Red Dress®—designed to warn women that heart disease is their number one killer. Since 2002, the Red Dress® has been a powerful symbol to millions of women like Norma who share a common desire to protect their hearts.

Norma and thousands of other residents living in cities with populations at high risk for heart disease continue to benefit from annual Heart Truth Road Show events where they can learn about their personal risk for heart disease and receive educational materials to help them take control of their heart health. By March 2009, 69 percent of women were aware that heart disease is the leading cause of death among women, up from 34 percent in 2000.

Introduction

As the Nation's medical research agency, NIH is a trusted source of information for millions of Americans. Communicating useful health and science information to the American public—a cornerstone of the NIH mission—requires integrative strategies that appeal to NIH's many audiences. The public has many faces: patients, family members, health care providers, scientists, public health workers, voluntary health organizations, policy leaders, and industry. To communicate effectively, NIH uses a variety of strategies and tactics to reach audiences where they are and in culturally competent, accessible ways.

Good communication achieves many goals toward improving health:

- Increasing knowledge and awareness of a health issue, problem, or solution
- Influencing perceptions, beliefs, and attitudes that may change social norms
- Prompting action
- Demonstrating healthy behaviors
- Refuting myths and misconceptions
- Helping forge self-sustainable relationships with communities

Each NIH IC shares a similar set of challenges: translating complex science into useful information and identifying and selecting appropriate communication outlets for key audiences. IC communications teams work directly with intramural and extramural scientists in their mission areas to ensure that the materials they produce are based on the soundest science.

The NIH Office of the Director's Office of Communications and Public Liaison (OCPL) provides an umbrella of leadership and guidance and coordinates communication activities across NIH ICs so the agency provides clear, consistent, and informative materials to the American public. NIH employs a range of strategies to reach Americans, and in particular, the agency continually assesses the most effective and efficient ways to reach those most vulnerable.

Public Information Campaigns and Communications Clearinghouses coordinate the ideas and actions of public and private organizations to reach people where they are. Clearinghouses are resource centers that connect the public with answers to their questions and that work with NIH ICs to develop new resources according to public need. Each year, NIH

distributes nearly 30 million science-based, health information publications to requestors who rely on NIH and its news stories, press releases, and publications for authoritative information. Information campaigns often package and deliver multiple communication products with the goal of either provoking a specific action or bringing about a behavioral change. NIH-sponsored health campaigns provide current, comprehensive, science-based information about the symptoms, diagnosis, and treatment of various diseases and conditions, often helping individuals to play a greater role in improving their health.

Each year, NIH distributes nearly 30 million science-based, health information publications to requestors.

Innovative Uses of Social Media that keep pace with modern technology enable NIH to connect with young and mobile audiences who rely nearly exclusively on electronic means of communication. Engaging and informative online resources—blogs, pod- and vodcasts, YouTube, wikis, and others—are powerful communication tools that NIH is using to reach crucial target audiences. NIH has created a presence with its portal for vodcasts and videos. NIH Vodcast episodes and the "NIH4Health" channel on YouTube reach millions of users each month.

Reliable, Authoritative, Accessible, Science-Based Health Information for a range of age groups is readily available online at the NIH health information portal. All NIH ICs continuously contribute scientifically vetted materials to this site, including information in easy-to-read formats and in languages other than English.

Cooperative Interactions with the Media enable NIH to provide the press with access to scientific and health expertise and a vehicle to tell health and science stories. In turn, programs that teach media literacy help impressionable youth deconstruct media messages so they can identify a sponsor's motives. Companion strategies guide communicators in composing messages attuned to the intended audience's point of view.

Partnerships with Outside Organizations help NIH achieve its mission to share and translate the results of medical research. Partnering activities also may include seeking entertainment industry support for a health issue. NIH routinely and freely shares materials with public health organizations, advocacy groups, schools, and community health officials, and encourages the personalization of health information based on individual and community needs.

Public Participation is a key part of NIH's ability to carry out its mission. NIH employs a multifaceted approach to public engagement and outreach. One approach is through the NIH Director's Council of Public Representatives (COPR)—a Federal Advisory Committee composed of up to 21 members of the public who provide the public's perspective into the NIH research priority-setting process as well as the agency's public health education and public engagement efforts. Through COPR, the agency connects directly with the public at the level of the NIH Director. The Council serves as the public's voice on issues relating to the NIH mission, informs the public of the research and health benefits gained through the public's investment in NIH, and helps NIH understand the public perspective and engage the public in NIH activities. Members of this group represent a wide variety of backgrounds based on geographic location, race, ethnicity, and experience, including patients, family members of patients, health care professionals, scientists, health and science communicators, and educators.

NIH's Council of Public Representatives serves as the public's voice on issues relating to the NIH mission, informs the public of the research and health benefits gained through the public's investment in NIH, and helps NIH understand the public perspective and engage the public in NIH activities.

NIH's "Clear Communication" effort builds upon sound research results provided by trans-NIH programs and activities. With this program, NIH aims to cultivate and contribute to a growing health literacy movement by increasing sharing of information including NIH educational products and research, lessons learned, and research in the area of health literacy. The program provides accessible materials and resources to help professionals reach individuals with literacy challenges,

Health Communication and Information Campaigns and Clearinghouses

as well as guidelines on how to create such materials. Sections on the Clear Communication website are devoted to health literacy, plain language, cultural competence, and NIH-funded health literacy research.

On a larger scale, NIH health communication programs move people from awareness to behavior change and are aimed at the societal level. Efforts to reduce drunk driving, for example, have changed individual and societal attitudes, behaviors, and policies through multiple forms of intervention, including communication. Groups with defined structures, such as associations, clubs, or civic groups, are important vehicles for carrying health messages and for creating and sustaining policy changes at the local level.

NIH also works diligently to develop and deliver transparent and timely information about funding practices and policies to ensure that the engine of medical research discovery runs at top speed and that the scientific workforce's information needs are met. NIH communicates regularly with the scientific community, including grantees, industry, and the scientific and academic press, to give them the sources and tools they need to access the latest research results and information.

Catalogs of Health Communication and Information Campaigns & Clearinghouses Activities

In response to the mandate under SEC. 403 (a)(4)(C)(ii) of the of the Public Health Service Act to provide a catalog of information clearinghouses, included here is a live link to a website featuring NIH's information clearinghouses. In response to the mandate under SEC. 403 (a)(4)(C)(iii) to provide a catalog of public education and information campaigns included here is a live link to a website featuring NIH's Education and Awareness Campaigns.

Summary of NIH Activities

NIH ICs are congressionally mandated to provide science-based health information to the public. As science and society change, the mode of information exchange needs to change, too. Near instant access to information through electronic media creates a new role for Federal agencies—trusted sources of credible information—to serve as a gateway for clear and balanced information about science and medicine, in a range of accessible formats.

New knowledge of human biology and advances in technology has given scientists the ability to better understand the language of human genes. This has thrust modern society into an age in which personalized medicine is nearing reality. That means that the results of modern scientific research are beginning to tell us how particular individuals will react to a medicine or a chemical in the environment, as well as which health problems they may be prone to. Having this individualized health information and understanding the role of cultural influences will enable Americans to implement prevention measures against a range of diseases and conditions.

A key aspect of the departure from "one-size-fits-most" medical care is individual involvement in health care and decision-making. Engaging the public in its own health is a crucial step toward achieving prevention-based medicine.

Delivering Health Information and Science News to the Public

Keeping the public informed about new developments in NIH-supported medical research is a primary goal of NIH health communication efforts. A variety of scientifically vetted, general health information and science news resources are available through NIH, including:

- *NIH Research Matters*, an e-column offering a glimpse into research accomplishments of NIH and NIH-funded scientists using brief, accessible stories that describe research results and put them in perspective
- "Research Results for the Public," a site that provides disease-by-disease descriptions of research progress and an interactive map of NIH research funding across the Nation
- "NIH & Clinical Research," a health information site that features podcasts, vodcasts, and radio programs in English and Spanish on clinical research
- *NIH News in Health*, a newsletter and online resource that provides practical and accessible health information monthly to public health workers, community centers, aging centers, voluntary health organizations, physicians, and hospitals

- “Talking to Your Doctor,” a site that offers NIH-produced resources from several ICs to enable patients to play an active role in their health care
- “The Women’s Health Resources Web Portal,” a site created to promote awareness and facilitation of research on women’s health by providing Web-based resources, including access to scientific literature and research reports, clinical trials opportunities, and consumer health information pertaining to women’s health

Because the press is a major source of health information for the public, NIH staff members work every day to provide background for media sources and identify key knowledgeable scientists to help reporters develop their stories. OCPL is the central coordinator and responder for media relations at NIH. In addition, to help the press interpret medical information with greater ease and accuracy, NIH also offers a highly acclaimed, free annual training course, "Medicine in the Media," now in its eighth year.

NIH also has developed a network of public information officers (PIOs) at academic institutions nationwide to ease communication, encourage collaboration, and coordinate publicity between NIH PIOs and communications staff at NIH-funded grantee and contracted institutions.

In our Internet-driven society, the Web and related media are indispensable sources of news. Recent research has shown that a majority of Americans who request NIH information not only use it, but also share it with others. More than 40 percent who use Web materials related to health take that information with them to their physicians’ offices. The NIH homepage, developed and managed by OCPL’s Online Information Branch, serves as entry point to the hundreds of individual NIH websites that comprise the NIH community of online programs, services, and information spanning thousands of health topics and research activities. One important page on the NIH website is "Get Involved at NIH" at <http://getinvolved.nih.gov/>, which serves as the NIH gateway for public participation, input, and feedback. Combined, the NIH websites, including those run by NLM, whose basic mission is to improve the dissemination of biomedical and health information, are accessed more than 3 billion times each year.

NIH and the Wikipedia Foundation are working together to make health and science information more accessible and reliable to the widest audiences possible.

In July 2009, NIH joined forces with the Wikimedia Foundation, the nonprofit, collaborative arm of Wikipedia®. Wikipedia is the international online encyclopedia that is the fourth largest Internet property. It attracts approximately 65 million visitors monthly and has information in 270 languages. NIH and Wikipedia are working together to make health and science information more accessible and reliable to the widest audiences possible. This historic "Academy" collaboration is the first of its kind for both organizations. NIH subject matter experts will contribute to Wikipedia and also help develop best practices for future sessions. Guidelines about how to contribute are available on the NIH website for scientists across the country. In addition, NIH communication offices have piloted use of social media for the past few years and will now implement newly released HHS social media guidelines to increase reach and to meet the audience where they are with added transparency and efficiency.

"i on NIH" is an Internet-based video program designed to educate and inform anyone interested in health-research news. For 30 minutes, once a month, i on NIH conveys the excitement of advances and important discoveries in medical research in a news-magazine style.

NIH Radio posts new stories each week to provide radio stations and the public with the latest information about NIH research findings, highlights of press conferences, and health campaigns. The NIH Radio News Service, now more than 20 years old, is available to millions of listeners on satellite radio through a feature called "NIH Health Matters," a 60-second spot aired on the HealthStar Radio Network and nearly 1,000 radio stations nationwide, including overnight airing on Washington, D.C.’s WTOP.

Health Communication and Information Campaigns and Clearinghouses

- "NIH Research Radio" is a biweekly podcast that can be listened to on a computer or downloaded into individual portable MP3 players.

To address the needs of those seeking more specific information about various diseases and conditions, NIH ICs produce a wide spectrum of more tailored science and health information in various formats, including the following selected examples:

- "Healthy Moments" is a radio series that provides tips to prevent and control diabetes, kidney disease, and related health disorders. The reports air on RadioOne's Majic 102.3 FM and two additional RadioOne, Inc. radio stations.
- The NIAMS Information Clearinghouse and the NIH Osteoporosis and Related Bone Diseases National Resource Center⁶⁴ produce and distribute health education materials in a variety of languages and formats on diseases and conditions of bones, joints, muscles, and skin to patients, health professionals, scientists, voluntary and professional organizations, and the media.
- NIH hosts online Picture and Video Galleries that showcase NIH-supported research results in vivid color and in motion. The images and videos illustrate various cutting-edge concepts in modern biomedicine and have been requested for use by *Discover* magazine and several textbook publishers.
- An annual "Medicine for the Public" lecture series has been presented every fall since 1978. The series provides the public with information on medical research geared in a lay-friendly format. The lectures are free and span a wide range of topics such as cancer screening, mental health, asthma, and many others.
- Various NIH ICs take advantage of commemorative days—for example, National HIV/AIDS Awareness Day—to publicize the importance of pressing health issues. Announcements from top NIH leadership are picked up by the media and highlight dozens of health diseases and disorders that affect the American public, offering timely opportunities and suggestions for prevention and treatment.
- In FYs 2008 and 2009, NIH added nearly 1.4 million articles from the biomedical journal literature to PubMed/MEDLINE, a vital tool for biomedical research, clinical medicine, and consumer health. The Indexing 2015 initiative is pursuing increases in the speed and efficiency of indexing through natural language processing and other automated techniques.

Reaching Different Audiences

On January 21, 2009, President Obama issued a directive to all Federal agencies calling for greater transparency, public participation, and collaboration. In response to this directive, and in keeping with the work that has already been done by NIH to encourage public input and provide the public with science-based health information and knowledge about the science it conducts and supports, the agency posted a Request for Information (RFI) to offer a new public input opportunity. NIH received an unprecedented response from both individual organizations and members of the public and will work with the results to enhance health information. Information gathered will help NIH develop and disseminate health, medical, and scientific information to a wider variety of audiences.

The agency anticipates using new outreach strategies and tools, including community-level outlets and Internet-based social media, to connect with the diverse American public that includes patients, families, friends, scientists, health professionals, public health workers, industry, health care providers, congressional staff, and voluntary organizations.

As America continues to diversify, NIH continues to gather input from communities and groups on cultural factors. This information is essential for the development of high-quality, tailored health information. Individuals and communities require culturally appropriate information on specific health conditions or concerns, and NIH ICs work hard to develop quality products to meet this need. For example, NIH harbors a special responsibility to serve America's youth through targeted approaches that address the needs and wants of modern children and teens. Four examples of how NIH is meeting the information requirements of specific audiences are:

- The NIH website continues to incorporate new technologies, including customized streaming news feeds such as Really Simple Syndication (RSS), Podcasting and Vodcasting, and health video posted on NIH's Facebook page,

YouTube, and Twitter sites, to reach the tech savvy segment of the population whose favored modes of communication are social media.

- *Control del dolor: Apoyo para las personas con cáncer (Pain Control: Support for People with Cancer)* are booklets produced in Spanish and English to address the needs of those suffering from cancer pain. They provide culturally sensitive information on cancer medicines and side effects, communication, pain control methods, and coping methods for the physical and emotional effects of pain.
- Four sets of heart health booklets offer motivation and action steps to incorporate heart healthy behaviors into daily life for Latino Americans and Filipino Americans. The booklets include references to culturally appropriate foods, activities, and situations.
- The NIH *MedlinePlus* magazine, and its bilingual Spanish counterpart *NIH Medline Plus Salud*, are quarterly consumer magazines focused on bringing the latest clinical findings to patients and their families. The magazines are complementary to the MedlinePlus and MedlinePlus en español websites, and are distributed to the public via doctors' offices nationwide.

The NIH website continues to incorporate new technologies, including customized streaming news feeds such as Really Simple Syndication (RSS), Podcasting and Vodcasting, and health video posted on NIH Facebook, YouTube, and Twitter sites.

NIH also keeps tabs on the health information needs of population groups that need specialized information, and NIH ICs proactively develop tailored communications products and approaches. These include science-based fact sheets, checklist resources, public service announcements, K-12 educational materials, and more, such as:

- In 2007 the Trans-NIH American Indian and Alaska Native Health Communications & Information Work Group, with representation from 16 NIH ICs, began working with the Indian Health Service's National Community Health Representative Program on activities of mutual interest. To help increase awareness of the vast array of resources provided by the NIH, the Work Group sends quarterly mailings of health information to a network of 1,600 Tribal community health representatives nationwide who serve as lay health educators and patient liaisons in Native communities.
- Since 2006, NIH, in collaboration with the Coalition for Imaging and Bioengineering Research, has hosted several campus tours each year aimed at introducing congressional staffers and patient advocacy group members to the cutting-edge research programs and laboratory facilities of NIH.
- Fifteen NIH ICs collaborated to develop the 43 health topics included on the popular www.NIHSeniorHealth.gov website, which covers health topics of particular interest to older adults such as Alzheimer's disease, cataracts, shingles, exercise, nutrition, fall prevention, taking medicines, and Medicare basics—all in a clear, easy-to-read format.
- Because African Americans are at high risk for developing heritable kidney disease, NIH developed and promoted *The Family Reunion Health Guide* for use at African American family reunions. This resource has everything African American families need to talk about the connection between diabetes, high blood pressure, and kidney disease.

NIH also is engaged in sustained NIH media and multicultural outreach efforts. Staff members produce 4 radio programs, including Spanish language programming, that feature public service announcements, 60-second reports, and long-format interviews. NIH also produces the award-winning podcast series "Pinn Point on Women's Health." The series highlights topics in women's health research through conversations with NIH experts on a variety of subjects, and breaking news on women's health research in a segment titled "Hot Flashes."

Rapidly Responding to Time-Sensitive Issues

New challenges arise constantly in our fast-paced world. Often, health communications need to be developed swiftly to raise awareness or encourage people to take urgent and specific actions based on a new finding or a health threat. In developing its communications programs, NIH remains vigilant to the need for timely communications materials. The following are selected examples from across NIH.

Health Communication and Information Campaigns and Clearinghouses

In 2009, a virus with clear pandemic potential, the 2009 H1N1 influenza virus, emerged. Because the scientific and public health communities had expected this scenario, NIH and HHS were poised to work collaboratively with other Federal agencies to prepare for a possible epidemic. In addition to a range of scientific and public health measures, NIH teamed with the U.S. Centers for Disease Control and Prevention (CDC) to provide consistent messaging in a coordinated and timely fashion for health consumers wanting the most up-to-date facts and guidelines about the 2009 H1N1 epidemic.

OCPL provides ongoing strategic and tactical advice on time-sensitive issues. The office works with NIH leadership, both in the OD and across NIH ICs, to ensure coherent, responsive messages. In 2009, OCPL was the focal point at NIH for communicating the impact of the American Recovery and Reinvestment Act (ARRA) by identifying and publicizing plans and funding opportunities. OCPL has been closely involved with the development of NIH processes for the agency's ARRA communication efforts.

Recognizing Problems and Taking Action

National data point to a serious crisis in that currently available health information is too difficult for average Americans to use to make health decisions.⁶⁵ The first ever National Assessment of Adult Literacy⁶⁶ determined that only 12 percent of U.S. adults had proficient health literacy, and more than a third of U.S. adults—77 million people—would have difficulty with common health tasks, such as following directions on a prescription drug label or adhering to a childhood immunization schedule using a standard chart.

The HHS Healthy People 2010 initiative established improving health literacy as a national health objective. Following the April 2004 Institute of Medicine report, *Health Literacy: A Prescription to End Confusion*, NIH issued a series of program announcements to encourage empirical research on health literacy concepts, theory, and interventions as they relate to public health priorities identified in Healthy People 2010.

A growing research base⁶⁷ is investigating how advances in knowledge about health literacy can inform intervention strategies and have an impact on quality of life and on the reduction of health disparities in general and special populations. Various approaches to addressing this vexing problem currently are underway, such as:

- Determining the effect of low-income parents' literacy levels on safety information comprehension and adoption of behaviors to prevent child injury
- Testing a literacy-focused program that provides educational assistance from pharmacists at the time of hospital discharge to people hospitalized with heart problems
- Identifying the spectrum of medical errors and adverse drug events in the elderly and how literacy affects medication safety
- Evaluating the relationship between informed consent, health literacy, and the documents and tools used to communicate with those who might participate in research studies
- Testing the effectiveness of a clinic-based health literacy intervention to improve initial and repeat use of colorectal and breast cancer screening in rural areas

An important component of solving health-related problems is identifying and understanding the context in which gaps in knowledge and communication arise and persist. For example, many dentists do not feel sufficiently trained to provide services to people with special needs. To help increase access to dental care, NIH developed a series of publications to equip general dentists and dental hygienists with information they need to deliver quality oral care to people with developmental disabilities.

A 2006 survey completed by NIH and the American Association of Retired People (AARP) revealed that nearly two-thirds of adults older than age 50 use complementary and alternative medicine, but only one-third of them share that information with their physicians—creating the potential for serious complications. NIH launched a new patient/provider education initiative, Time to Talk, which encourages open discussion of all health care practices to ensure safe and coordinated care.

Although the life expectancy of the American people has reached a historic high, along with it has come an increase in the number of people living with, and dying from, chronic debilitating diseases. By communicating to the public and the media the results of its important research in this area, NIH provides timely and helpful information to family members and loved ones of the dying.

By communicating to the public and the media the results of its important research on end-of-life, NIH provides timely and helpful information to family members and loved ones of the dying.

Rethinking Drinking, a new website and downloadable booklet, aims to help many people reduce their risk for alcohol problems, a serious societal issue. The new materials present evidence-based information about risky drinking patterns, the alcohol content of drinks, the signs of an alcohol problem, along with information about medications and other resources to help people who choose to cut back or quit drinking.

As the American population ages, the Nation's disease burden is shifting toward conditions that affect older people. Building on the success of an earlier award-winning partnership with Home Box Office (HBO), in 2009, NIH and HBO copresented the multiplatform public health series, "The Alzheimer's Project," to help widen public understanding of this disease that affects millions of people and their caregivers.

In 2009, NIA and HBO co-presented the multi-platform public health series, The Alzheimer's Project, to help widen public understanding of this disease that affects millions of people and their caregivers.

Many urgent health issues continue to remain "under the radar," unduly affecting vulnerable groups. For example, chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States. NIH developed the COPD: Learn More Breathe Better® Campaign, which encourages people at risk to get a simple breathing test and talk to their doctors about treatment options.

Partnering With Outside Organizations

NIH ICs receive regular input from a wide range of outside organizations, and when appropriate, engage in strategic partnerships and collaborations that can enhance NIH's ability to carry out its mission as the Nation's medical research agency. Partners include nonprofit groups, such as voluntary health agencies and community-based organizations. These groups can increase the reach of NIH health communications and outreach programs. Agency interactions with such groups range from routine meetings to the establishment of novel programmatic initiatives and partnerships that can include co-funding of research. These efforts are an important way for NIH to receive regular input from its public constituencies and to forward research announcements, research results, agency news, and scientific press releases.

Examples of projects involving NIH ICs and non-profit organizations include:

- NCI's Community Networks Program, which is designed to reach communities and populations that experience a disproportionate share of the cancer burden. These include African Americans, American Indians/Alaska Natives, Hawaiian Natives and other Pacific Islanders, Asians, Hispanics/Latinos, and underserved rural populations. Strategic partnerships and collaborations enhance vital training, research, and educational functions of this program.
- NIMH's Outreach Partnership Program, which joins with national and state organizations to bridge the gap between research and clinical practice. The program helps disseminate the latest scientific findings; inform the public about mental disorders, alcoholism, and drug addiction; and reduce the stigma and discrimination associated with these illnesses. NIMH has established a formal process to ensure consistent, open dialogue with its major stakeholders through regularly scheduled meetings between their representatives and the NIMH Director and senior staff.
- The NIAMS Health Partnership Program, a community-based, collaborative research program between NIAMS and Washington, D.C., area community organizations. Through research with underrepresented patients affected by arthritis and other rheumatic diseases, the program studies health disparities and their causes and provides direction for improving the health status and outcomes of affected minority communities. Its Community Health Center,

Health Communication and Information Campaigns and Clearinghouses

located in the Columbia Heights area of northwest Washington, D.C., gives the community access to specialized care and health information, and provides NIH researchers with access to patients most affected by rheumatic diseases.

- NIEHS's Partnership for Environmental Public Health, which brings together scientists, community members, educators, health care providers, public health officials, and policy makers. A hallmark of this program is that communities are actively engaged in all stages of the research, dissemination, and evaluation. This ensures that vital information about linkages between exposures and disease can be discovered and used to promote health and reduce the risk of disease across the populations at highest risk.
- The NIDCR-hosted annual Patient Advocates Forum, which brings together voluntary health organizations with a shared interest in the oral health effects of their respective disorders and conditions. Begun in 2000, the forum provides an opportunity for NIH to solicit input from the public on a range of NIDCR activities and policies, and to keep the advocacy groups informed about ongoing and planned research programs of particular interest to their constituencies.

Where appropriate, NIH ICs partner with the private sector to reach target audiences and achieve agency health communication goals. Examples of projects involving NIH ICs and the private sector include:

- The NEI Health Education Program Partnership, which consists of more than 70 public and private national organizations interested in eye health education. The purpose of the partnership is to establish ongoing, interactive, mutually beneficial relationships with the NEI and other organizations to facilitate collaboration; to exchange information, views, and materials on eye health education; and to identify and target audiences at higher risk of eye diseases and conditions.
- The Bethesda Hospitals' Emergency Preparedness Partnership, a unique team of emergency responders from Federal, military, and private health care agencies. This partnership joins the NLM with three hospitals in close proximity—the NIH CC, the National Naval Medical Center, and Suburban Hospital—to integrate and leverage resources for local, regional, or national emergencies. Among the group's activities are periodic disaster drills.
- The National Diabetes Education Program, which is co-led by the NIDDK and CDC, works with more than 200 partners at the Federal, State, and local levels to improve the treatment and outcomes for people with diabetes, promote early diagnosis, and prevent or delay the onset of type 2 diabetes. Partners include professional associations, national service and civic organizations, and community groups.

Outreach to the Scientific and Research Communities

In addition to communicating science and health news and information to the public, NIH reaches out to the scientific and research communities to share information and obtain input. Many of these communications campaigns are essential elements in the development of science policies that fit the needs of the NIH audiences that extend beyond researchers to include patients and advocacy groups that are vital participants in the research enterprise. For example, through one recent outreach effort, NIH obtained critical input that informed the agency's issuance of the NIH Stem Cell Guidelines in July 2009.

In addition to communicating science and health news and information to the public, NIH reaches out to the scientific and research communities to share information and obtain input.

In other outreach activities, NIH developed and disseminated timely information about several pressing issues relevant to the scientific community, such as enhancements to the peer review process and new opportunities and requirements resulting from implementation of ARRA.

NIH continues to partner with the ResearchChannel consortium, a public service organization that broadcasts the latest research information free-of-charge, 24 hours per day through satellite and cable television systems—providing access to more than 30 million U.S. subscribers. Much like C-Span communicates political developments to a broad public audience, the ResearchChannel provides wall-to-wall coverage through DIRECTV of nothing but research. The channel also is available on 70 university and school-based cable systems in the United States and overseas.

NIH leads by example in addressing scientific workforce-related issues, and communication about these problems is a key element toward finding tractable solutions. In December 2008, NIH hosted the largest national conference ever on health

disparities—the first summit of its kind that involved all NIH ICs and brought together more than 4,000 national and international clinicians, researchers, policy leaders, academicians, and community leaders. The conference spurred new lines of communication among researchers, spanning a broad range of fields and strategies related to combating health disparities and addressing the companion problem of low health literacy.

Following the release of the National Academies report, *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, NIH created a Working Group on Women in Biomedical Careers. Co-chaired by the NIH Director and ORWH Director, the group is currently working to address recommendations from two conferences held on the topic: "The National Leadership Workshop on Mentoring Women in Biomedical Careers," and "Women in Biomedical Research: Best Practices for Sustaining Career Success." NIH continues to spread the word about the meeting proceedings and their impact on the broader scientific community.

As a world health leader, NIH also must extend its reach to the international scientific community. NIH develops new partnerships among U.S. scientists, institutions, and counterparts abroad to advance research and training in the biomedical and behavioral sciences. The partnering activities foster communications about health and research needs and thus identify opportunities for collaboration with foreign science-funding agencies, the U.S. Department of State, U.S. technical agencies, and international organizations.

Several ICs have developed focused communications tools to provide assistance to, and enable bidirectional communication with, the scientific community and grantees in particular, such as:

- In 2009, NIGMS changed its *Feedback Loop* electronic newsletter, which had been published 3 times a year since 2005, into a blog that posts news and other information as it happens. Site users can submit comments and ask questions, which Institute staff answer. This interactive approach has been especially helpful in communicating time-sensitive information about ARRA.
- The "NCRR e-Reporter" fosters communication, collaboration and resource sharing in areas of current interest to scientists and the public. More than 2,400 subscribers include NCRR grantees, as well as other stakeholders in research, such as leaders in academia, industry, voluntary health organizations, patient advocacy groups, scientific professional societies, policy makers, and science teachers.
- The "NEI Pipeline" is an e-mail broadcast service intended to keep the vision research community informed of grant opportunities, new initiatives, and other newsworthy information concerning NEI and NIH.
- "NIH Grant Cycle: Application to Renewal," produced by NIAID, is an online tutorial that combines graphics and text to explain how to successfully compete for an NIH grant. A reinvention of NIAID's "All About Grants" tutorials, the new resource divides the funding lifecycle into 12 phases and offers stage-specific information and advice for scientific investigators.
- OCPL developed a constituency database, which contains approximately 400 contacts for advocacy organizations, colleges and universities, hospitals and research centers, and professional societies. Approximately 10 to 12 emails are distributed to this list annually, on topics such as the NIH Peer Review Enhancement Effort; the Research, Condition, and Disease Categorization system; Public Access Policy; and relevant scientific meetings.

Conclusion

In this exciting and quickly evolving era of modern science, NIH has the responsibility—and the privilege—of finding novel ways to connect with the American public. This challenge goes beyond unidirectional delivery of health-related materials, since education involves much more than understanding information. Rather, this urgent task invites a dialogue with the general public, scientists, health care providers, and policy makers to assess what people know, what they want to know, and how to meet those needs of varied audiences. Bringing science to life through innovative materials and programs is a proud tradition of NIH. Thus, NIH continues to employ a wide variety of communication vehicles and makes information available through cutting-edge and audience-tested outlets and strategies.

Clear, yet savvy, health communication approaches are paramount to helping people take advantage of research advances to improve their health.

Health Communication and Information Campaigns and Clearinghouses

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research

I = Supported through **I**ntramural research

O = **O**ther (e.g., policy, planning, or communication)

COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program

GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct

ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Delivering Health Information and Science News to the Public

Disseminating Evidence-Based Health Information on Diabetes and Digestive and Kidney Diseases: The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational materials on diabetes and kidney disease, respectively. For example, the NDEP encourages people to take "small steps" to prevent type 2 diabetes. The NDEP also promotes the importance of comprehensive diabetes control in its Control Your Diabetes. For Life educational campaign. The NKDEP encourages African American families to discuss kidney disease at family reunions, and also provides tools and resources for health care providers to help coordinate care and improve patient outcomes for kidney disease. Both programs tailor materials for minority groups at high risk. Information Clearinghouses also provide key health information for patients, health care professionals, and the general public. A recent campaign highlighted the importance of using accurate methods to test hemoglobin A1c in people with diabetes who have sickle cell trait or other inherited hemoglobin variants. Other recent campaigns raised awareness of celiac disease and interstitial cystitis. The Weight-Control Information Network provides up-to-date, science-based information on weight control, obesity, physical activity, and related nutritional issues.

→ For more information, see <http://www2.niddk.nih.gov/HealthEducation/>

→ For more information, see <http://ndep.nih.gov/>

→ For more information, see <http://nkdep.nih.gov/>

→ For more information, see <http://win.niddk.nih.gov/>

→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*

→ (E) (**NIDDK**, CDC)

New Publications on Mental Health Disorders: NIH has developed several new mental health publications, including booklets and fact sheets on attention deficit hyperactivity disorder, panic disorder, obsessive compulsive disorder, bipolar disorder, bipolar disorder in children and teens, post-traumatic stress disorder, anxiety disorders, mental health medications, and a participants' guide to mental health research. Several of the publications also are available in Spanish and easy-to-read versions.

→ For more information, see <http://www.nimh.nih.gov/health/publications/index.shtml>

→ (O) (**NIMH**)

NIDCD Information Clearinghouse: NIDCD's Information Clearinghouse disseminates free health information in the areas of hearing, balance, smell, taste, voice, speech, and language to inquiring members of the public. For the years 2008-2009, the NIDCD Information Clearinghouse has maintained a toll-free phone and TTY number for the public and has ensured that NIDCD publications remain current and timely by adding or updating bilingual fact sheets and other

educational materials for dissemination to the public. On average, the clearinghouse distributes 250,000 materials each year. In addition, the clearinghouse disseminates NIDCD health information materials at more than 28 professional conferences and health fairs around the country. Clearinghouse staff also have assisted in the planning and implementation of NIDCD's new campaign against noise-induced hearing loss, *It's a Noisy Planet. Protect Their Hearing.*

- For more information, see <http://www.nidcd.nih.gov/health/>
- (O) (NIDCD)

The Genetic and Rare Diseases Information Center (GARD): Since 1989, repeated studies and panels found that patients and families, as well as physicians, had great difficulties obtaining needed information about the almost 7,000 rare diseases known today. Then NIH established GARD. Since its inception more than 7 years ago, the information center has provided approximately 24,102 individualized responses about 6,497 different rare and/or genetic diseases. On January 30, 2008, GARD introduced new online information resources about rare and/or genetic diseases on the ORDR website for the public. Now, when a person submits a question to GARD about a particular condition, the question is edited and de-identified to ensure confidentiality and posted with its answer to the disease webpage on the ORDR website. A list of resources also is added to each disease webpage for additional information. Information specialists remain available to assist users directly and answer questions in both English and Spanish by telephone, e-mail, mail, or TTY. In the first year, visits to the webpages quadrupled from an average of 500 visits to 2,000 visits per month and continue to increase steadily. Given that the number of visitors and visits to the webpages continues to increase, with more than 250,000 additional individuals using the services of the information center, the sustained lower direct inquiry volume suggests that people are finding answers to their questions on the new Web disease pages without requiring the personal assistance of information specialists.

- For more information, see <http://rarediseases.info.nih.gov/GARD/>
- For more information, see <http://rarediseases.info.nih.gov/>
- (O) (ODP/ORDR, NHGRI)

Genetics Home Reference (GHR) and GeneTests: GHR is an online resource created for the general public that provides basic information about genetic conditions and the genes and chromosomes related to those conditions. In FYs 2008 and 2009, the system was expanded to include information on 200 more genetic conditions and 200 more genes. The website now covers more than 400 genetic conditions, more than 600 genes, all the human chromosomes, and information about disorders caused by mutations in mitochondrial DNA. GHR also links to GeneTests, a resource developed for health care professionals that provides current, authoritative information on genetic testing and is used in diagnosis, management, and genetic counseling. In addition to peer-reviewed disease descriptions, GeneTests includes voluntary listings of laboratories offering in-house testing and clinics providing genetic evaluation and genetic counseling. GeneTests is designed to promote the appropriate use of genetic services in patient care and personal decision making.

- For more information, see <http://ghr.nlm.nih.gov>
- For more information, see <http://www.ncbi.nlm.nih.gov/sites/genetests>
- (I) (NLM, NHGRI)

Exhibitions for the Public: NIH continues to present lively and informative exhibitions that enhance the awareness and appreciation of science, medicine, and history. *Visible Proofs: Forensic Views of the Body* closed in February 2008 after a highly successful 2-year run. A new exhibition, *Against the Odds: Making a Difference in Global Health*, which looks at the revolution in global health that is taking place in towns and cities around the world, opened in FY 2008 and will continue through FY 2010. An exhibit titled *Harry Potter's World: Renaissance Science, Magic, and Medicine* also opened in 2008. Using historical materials from the NIH, this exhibition explores Harry Potter's world and its roots in Renaissance magic, science, and medicine. Scores of school groups and other organizations visit the exhibitions each year, and many more are able to access the accompanying online versions. Through a Traveling Exhibitions program, traveling

Health Communication and Information Campaigns and Clearinghouses

versions of the exhibits also are made available to libraries across the Nation after they close at NIH, with six exhibits currently included in this program.

- For more information, see <http://www.nlm.nih.gov/hmd/about/exhibition/>
- (I) (NLM)

Linking Research Advances to NIH Funding: NIGMS publishes a monthly electronic newsletter, *Biomedical Beat*, that highlights recent research advances made by grantees and features cool scientific images. Through this and other activities, the Institute works to make connections between NIH grant funding and research advances by scientists at universities, medical schools, and other institutions.

- For more information, see <http://publications.nigms.nih.gov/biobeat>
- (O) (NIGMS)

MedlinePlus and MedlinePlus En Espanol: MedlinePlus and the Spanish language MedlinePlus En Espanol provide access to high-quality consumer health information on more than 800 diseases and conditions, with authoritative information from NIH, other government agencies, and health-related organizations. Enhancements in FYs 2008-2009 included improved search capabilities and addition of summary information. Content also was expanded to include information in more than 40 languages, addressing the growing needs of non-English-speaking patients. Go Local links from MedlinePlus, developed in partnership with libraries across the country, enable users to find relevant health services in local geographic areas. The number of Go Local sites increased to 34 in FY 2009, covering 46 percent of the U.S. population. The *NIH MedlinePlus Magazine* transmits the latest useful research findings in lay language, with feature stories on topics such as colorectal cancer, post-traumatic stress disorder, and childhood diseases. More than 600,000 copies of the magazine were distributed free to physician offices in FY 2009, up from 50,000 in FY 2006. In addition, a Spanish language edition, *Salud!*, was launched in FY 2009, as were online versions of both English and Spanish language magazines.

- For more information, see <http://www.medlineplus.gov>
- For more information, see <http://medlineplus.gov/spanish>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (I) (NLM)

Reaching Different Audiences

Education and Outreach: NCI's Office of Communications and Education (OCE) provides comprehensive cancer information to those at risk and to patients, caregivers, and health care providers. This information ranges from prevention, through treatment, to end-of-life topics. For example, clinical sites across the country extensively use NIH print- and Web-based materials to support their educational programs. OCE also provides public affairs, publications, audiovisual exhibits, and Web development support to NCI Divisions, Offices, and Centers. The Cancer Information Service (CIS) effectively communicates information through a Partnership Program to help reach those with limited access to health information; an Information Service that provides cancer information by telephone, TTY, instant messaging, and e-mail; and a Research Program that helps advance health communication practices.

- For more information, see <http://www.cancer.gov/aboutnci/oce/>
- For more information, see <http://cis.nci.nih.gov/>
- For more information, see <http://cancer.gov/publications>
- For more information, see <http://www.cancer.gov/cancertopics>
- For more information, see <http://www.cancer.gov/espanol>
- This example also appears in Chapter 2: *Cancer*
- (E) (NCI)

Exercise Guide for Older Americans: In January 2009, NIH offered an update of its popular exercise guide, newly titled *Exercise and Physical Activity: Your Everyday Guide from the National Institute on Aging*. The guide is the result of a 2-year process overseen by the Task Force on Exercise and Physical Activity, which included top scientists conducting research on exercise and physical activity in older adults, as well as representatives from key organizations involved in promoting exercise and physical activity to the public, including CDC, the American College of Sports Medicine, and the International Council on Active Aging. Based on an intensive review by these experts of the evidence on physical activity, the updated publication reviews in lively, easy-to-understand language the benefits of physical activity for older people, discusses the importance of regular effort and goal setting, provides specific activities and exercises appropriate for varying strength and skill levels, and includes worksheets to help the reader track his or her progress. The new guide is proving popular already with the public; between 2000 and 2008, NIH distributed 1.2 million copies while in 2009, NIH has distributed more than 300,000 copies of the guide. NIH is undertaking an outreach effort on exercise, with the guide as a foundation, to encourage older people to become more physically active.

- For more information, see <http://www.nia.nih.gov/Exercise>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (O) (NIA)

Health Information for Older Adults: NIH maintains a comprehensive program of health information aimed at older Americans. The NIA Information Center maintains a website and toll-free telephone lines to provide information in English and Spanish aimed at maintaining and improving health. Age Page fact sheets offer comprehensive, easy-to-read information on nearly 50 topics. The research update Spotlight on Aging Research (SOAR) provides current information on health and NIA activities to the public, policymakers, and researchers. The NIHSeniorHealth website enables the growing number of "wired seniors" to find credible aging-related health information in an online format that is compatible with their cognitive and visual needs, as determined by NIH-supported research; it includes 42 health topics developed by 12 NIH Institutes and one topic contributed by the Centers for Medicaid and Medicare. NIH also has developed a senior-friendly curriculum for people who train older adults to use computers. The Alzheimer's Disease Education and Referral (ADEAR) Center is the Federal government's primary source of information for patients, caregivers, health providers, policymakers, and the general public on Alzheimer's disease- and age-related cognitive change. The Center maintains a national database of clinical trials and develops easy-to-read materials in English and Spanish. In 2009, NIH collaborated with HBO Documentary Films, in association with the Alzheimer's Association, Fidelity Charitable Gift Fund, and Geoffrey Beene Gives Back Alzheimer's Initiative, on The Alzheimer's Project, which featured four documentary films, 33 supplemental films, a website, and a community-based information and outreach effort, with a companion book.

- For more information, see <http://www.nia.nih.gov/Alzheimers>
- For more information, see <http://www.nia.nih.gov/HealthInformation/Publications>
- For more information, see <http://www.NIHSeniorHealth.gov>
- (E) (NIA, NLM)

Know Stroke Efforts and New Stroke Slogan: In 2004, NIH entered a partnership with CDC to launch a grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders who work as "Stroke Champions" to educate their communities about the signs and symptoms of stroke and the need for immediate action. The program focuses on reaching African Americans, Hispanics, and seniors in communities that have the health care systems in place to treat stroke. To date, the program has been implemented in 12 cities, educating 184 Stroke Champions who have conducted more than 600 community events. The program was expanded this year to Charleston, South Carolina, and, as a follow-up to that program, materials will be developed for coastal communities with unique dialects. NIH also recently expanded its public education programs by collaborating with the Brain Attack Coalition (BAC) to develop a new action-oriented message that all member organizations could use with their current stroke awareness efforts. The BAC is a group of organizations committed to stroke prevention and treatment

Health Communication and Information Campaigns and Clearinghouses

chaired by NINDS. The new slogan—"Stroke strikes fast. You should too. Call 9-1-1."—was launched in May 2009 during Stroke Awareness Month.

- For more information, see <http://stroke.nih.gov/about/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Minority Health and Health Disparities*
- (O) (NINDS)

Medicine in the Media Course: NIH presents a free annual training opportunity to help journalists evaluate and report on medical research. The program was created to address a growing need to improve the reporting of scientific and medical research findings by the media. Now in its eighth year, the course examines the challenges and opportunities inherent in the process of communicating the results of medical research to the public. The interactive program lays out the critical basics of differentiating strong from weak scientific information, well-designed vs. poorly-designed scientific studies, and "strength of opinion vs. strength of evidence." Stressing an evidence-based approach and re-examining intuitive beliefs about medicine, the course prepares participants for the crucial task of interpreting and evaluating research findings, including methods to select stories with meaningful messages for the public and place them in the appropriate context. Sessions are interactive, with hands-on opportunities to apply lessons learned, and incorporate journalists' unique perspectives on the public's need for useful medical knowledge. The program is highly competitive and attracts media and journalism professionals from around the country for a 3-day intensive workshop. Feedback from participants indicates that the program changed their fundamental understanding of what is worthy of reporting and helped them to provide appropriate context regarding the strengths, weaknesses, and relevance of a given study's findings. Participants frequently recommend the program to colleagues.

- For more information, see <http://medmediacourse.nih.gov/>
- For more information, see http://medmediacourse.nih.gov/02_agenda.html
- (E) (ODP/OMAR)

National Child and Maternal Health Education Program (NCMHEP): To develop a national maternal and child health education program with input from stakeholders, NIH created a program to effectively review and translate maternal and child health research findings into new knowledge that can be disseminated to clinicians and their patients. Forums have been created in which major stakeholders in maternal and child health can work together to review scientific findings and decide how to best communicate their findings to targeted audiences. NIH has identified four areas on which the NCMHEP will focus: prematurity and low birth weight, pediatric obesity, infant mortality, and environmental influences on child health and development.

- (O) (NICHD)

SIDS Outreach in Minority Communities: Since 1994, when NIH launched its campaign to reduce the risks of Sudden Infant Death Syndrome (SIDS), overall SIDS rates have declined significantly, yet the disparities continue to exist. Today, babies in the American Indian and Alaska Native communities are twice as likely to die from SIDS as white infants. To help eliminate this disparity, NIH, in collaboration with Native American Management Services, Inc., developed adaptable, culturally appropriate SIDS risk-reduction materials for use in five Indian Health Service Areas—Northern Tier-Aberdeen, Billings, Bemidji, Portland, and Alaska. Under the guidance of a community-based work group, educational materials have been developed based on recommendations from the five areas. The outreach project is called "Healthy Native Babies: Honoring the Past, Learning for the Future." Project materials include a training manual and a CD-ROM. The interactive CD-ROM that has been developed includes templates for a variety of SIDS risk-reduction educational materials. It contains photographs of American Indian and Alaska Native families and infants from the five regions, taken by local photographers. These photographs can be incorporated into educational materials such as posters, flyers, brochures, and postcards.

- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (O) (NICHD)

Science Education Partnership Award (SEPA) Program: SEPA increases the public's understanding of medical research by: 1) increasing the pipeline of future scientists and clinicians, especially from underserved and rural kindergarten to grade 12 (K-12) students, and 2) engaging and educating the general public on health-related advances made possible by NIH-funded research. By creating relationships among educators, museum curators, and medical researchers, SEPA encourages the development of hands-on, inquiry-based curricula that inform subjects about timely issues, including obesity, diabetes, stem cells, and emerging infectious diseases. Additionally, SEPA projects are designed to enhance public trust by focusing on topics such as the clinical trials process, patient safeguards, and medical research ethics. Through SEPA exhibits at science centers and museums, the program provides educational and community outreach activities to tens of thousands of people every year. In FY 2008, SEPA supported 68 projects, of which 50 targeted middle- and high-school students and 18 were based in science centers and museums.

- For more information, see <http://www.ncrr.nih.gov>
- For more information, see <http://www.ncrrsepa.org>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NCRR)

National Network of Libraries of Medicine (NN/LM): With more than 5,800 full and affiliate members representing academic health sciences libraries, hospital libraries, public libraries, and community-based organizations, the NN/LM plays a pivotal role in NIH's outreach programs to reduce health disparities and improve health information literacy. In FYs 2008-2009, NIH funded more than 400 community-based projects to enhance access to health information for health disparity and other medically underserved populations, building upon longstanding relationships with institutions providing health-related services and information to health disparity populations and developing many new relationships with schools, churches, public health departments, and others interested in improving health literacy and information access. Projects took place in rural and inner city communities and special populations in 35 states and the District of Columbia. The NN/LM also is a key player in the MedlinePlus "Go Local" service, which provides information about local community services to complement the nationally applicable health information in MedlinePlus. Go Local coverage reached 46 percent of the U.S. population in FYs 2008-2009. With an excellent track record of providing access to health information for clinicians and patients displaced by disasters, the NN/LM is the backbone of NIH's strategy to promote more effective use of libraries and librarians in local, State, and national disaster preparedness and response efforts. In FY 2008, a major initiative was the development of a national NN/LM Emergency Preparedness Plan to ensure backup health library services in the aftermath of a disaster and establish librarians as key community resources in disaster planning and response.

- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NLM)

Minority Health Information Access: An NIH outreach goal is to reduce health disparities among African American, Hispanic, and Native American populations by using a variety of approaches to promote access to and use of health information among diverse communities. The Historically Black Colleges and Universities (HBCU) ACCESS Project, developed in partnership with the United Negro College Fund Special Programs, provides technical assistance, training, and funding for locally developed projects incorporating the use of NIH information resources in HBCU campuses and communities. The Environmental Health Information Partnership enhances the capacity of 20 academic institutions that provide health-related services and information to health disparity populations by supporting their efforts to reduce health disparities through the access and use of environmental health information. Projects to increase the knowledge of Native Hawaiian community members about health information were completed at the community of Miloli'i and Waimanolo

Health Communication and Information Campaigns and Clearinghouses

Health Center. At Cankdeska Cinkana Tribal College, Spirit Lake Nation, a health-related education program was developed along with tribal library improvements. Specialized websites, developed and expanded in partnership with community representatives, collect and organize information for specific populations such as Asian Americans, American Indians, and peoples of the Arctic. In the Lower Rio Grande Valley, the VIVA! Peer Tutors program at a magnet health high school is an award-winning effort to involve high school students in teaching their peers about online health information. The project has been extended to other schools and expanded to include promotion of health careers.

- For more information, see <http://sis.nlm.nih.gov/outreach.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (I) (NLM)

Rapidly Responding to Time-Sensitive Issues

Guidelines for the Medical Management of HIV: HHS issues Federal guidelines for the medical management of HIV infection and its associated co-infections, including antiretroviral treatment of HIV disease, prevention and treatment of opportunistic infections, and prevention of mother-to-child transmission of HIV. The guidelines are written, reviewed, and updated by working groups of the NIH OAR Advisory Council made up of HIV experts from across the country, including physicians, pharmacists, researchers, and community representatives. The guidelines represent the state of knowledge regarding the medical management of HIV disease in the United States. As the introduction and/or availability of new therapeutic agents, new clinical data, and emerging disease threats may change therapeutic options and preferences rapidly, the guidelines are updated frequently and are available as a "living document" on the *AIDSinfo* website. Updates that recently were added to the *AIDSinfo* website include the *FDA Alert: Use of Antivirals Tamiflu and Relenza in Children* and the *CDC Interim Guidance-HIV-Infected Adults and Adolescents: Considerations for Clinicians Regarding Novel Influenza A (H1N1) Virus*.

- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (O) (OAR)

Recognizing Problems and Taking Action

It's a Noisy Planet. Protect Their Hearing: Approximately 26 million American adults are estimated to have high-frequency hearing loss caused by exposure to noise at work or during leisure activities. Since 1999, NIH has collaborated with the National Institute for Occupational Safety and Health on WISE EARS!®, a national education campaign to increase awareness about noise-induced hearing loss among the public and workers. In October 2008, NIH expanded these efforts by launching It's a Noisy Planet. Protect Their Hearing. This new campaign is designed to increase awareness among parents of children ages 8 to 12—or tweens—about the causes and prevention of noise-induced hearing loss. With this information, parents and other adults can encourage children to adopt healthy habits that will help them protect their hearing for life.

- For more information, see <http://www.noisyplanet.nidcd.nih.gov>
- (O) (NIDCD)

Providing Science-Based Oral Health Information: NIH provides science-based oral health information tailored to meet specific needs. Two examples are described here.

- *Practical Oral Care for People with Developmental Disabilities:* Finding dental care in the community is challenging for people with developmental disabilities. Many dentists do not feel trained sufficiently to provide services to people with special needs. To help increase access to dental care, NIH developed a series of publications to equip general dentists with information they need to deliver quality oral care to persons with developmental disabilities. The series includes continuing education (CE) programs for dentists and dental hygienists and a guide for caregivers describing

their important role in maintaining good oral health for their family member or client. The modules are so popular that NIH has extended the CE credit through 2011.

- *Spanish-Language Oral Health Website:* The Special Care Dentistry Association partners with NIH in this important health education outreach—Spanish-Language Oral Health Website. This new Spanish-language website tailored for U.S. Hispanics/Latinos increases Spanish speakers' access to science-based oral health information. The site recently was tested in two cities; participants were Spanish-dominant and bilingual Latinos with backgrounds from different countries of origin and with varying levels of education. The test was to ensure the new website is understandable, credible, and attractive to the intended audience. Other goals included understanding the approach Latinos take when seeking health information online, what they think of the quality of online health information, and whether there are significant differences between Spanish-dominant and bilingual individuals.
 - For more information, see <http://www.nidcr.nih.gov/OralHealth/Topics/DevelopmentalDisabilities/>
 - For more information, see <http://www.nidcr.nih.gov/espanol>
 - This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Minority Health and Health Disparities*
 - (O) (NIDCR, NICHD)

Reaching Out to Teens and Health Care Professionals: In the spring of 2009, NIDA unveiled NIDAMED, its first comprehensive physicians' outreach initiative. NIDAMED gives medical professionals a variety of information, including tools and resources, to help in screening patients for tobacco, alcohol, and illicit and nonmedical prescription drug use. The NIDAMED website contains links to numerous resources for health care professionals: an online screening tool titled NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NM ASSIST); two guides for clinicians (quick reference and a comprehensive resource guide); a number of key NIDA publications, such as the *Principles of Drug Abuse Treatment: A Research-Based Guide*, *The Science of Addiction*, a *Commonly Abused Drugs Chart*, and a postcard that encourages patients to "Tell Your Doctor About All the Drugs You Use." The NIDAMED initiative stresses the importance of the patient-doctor relationship in identifying and intervening early in patients' drug use behaviors before they evolve into life-threatening conditions. NIH is planning to hold its third annual Drug Facts Chat Day in November 2009. These events let students and teachers in classrooms across the United States ask questions of the Nation's top experts in the field of drug abuse and addiction. NIH staff will gather in a computer lab on the event day and will respond to submitted questions in real time. Chat Day events have proven to be a resounding success. The inaugural event elicited more than 35,000 questions.

- For more information, see <http://www.nida.nih.gov/nidamed>
- For more information, see <http://www.nida.nih.gov/scienceofaddiction>
- For more information, see <http://www.drugabuse.gov/chat>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIDA)

Rethinking Drinking: To help people recognize and reduce their risk for alcohol problems, NIH recently launched an interactive website and supporting booklet, *Rethinking Drinking*. These new NIH resources offer evidence-based information about risky drinking patterns, the alcohol content of drinks, and the signs of an alcohol problem, along with information about medications and other resources to help people who choose to cut back or quit drinking. The website also provides tools, such as calculators that can be personalized by the user to estimate the alcohol content in common cocktails.

- For more information, see <http://rethinkingdrinking.niaaa.nih.gov>
- (E, O) (NIAAA)

Health Communication and Information Campaigns and Clearinghouses

Children and Clinical Studies: Medical research in children has saved lives and improved health and well-being, yet parents often are reluctant or uncertain about allowing their child to participate in a clinical study. The Children and Clinical Studies campaign helps parents and others to learn more about how clinical research is conducted in children, so that they can make well-informed decisions about whether to participate. Its website, which is available in English and Spanish, combines practical information with award-winning video footage of parents, health care providers, and children themselves discussing the rewards and challenges of participating in research. Educational materials for parents and health care providers can be requested through the site, as well.

- For more information, see <http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php>
- This example also appears in Chapter 3: *Technology Development*
- (E) (NHLBI, NCRR, NICHD)

Partnering with Outside Organizations

Disaster Information Services: A Disaster Information Management Research Center was established in FY 2008 with the aim to facilitate access to disaster information, promote more effective use of libraries and disaster information specialists in disaster management efforts, and ensure uninterrupted access to critical health information resources when disasters occur. A disaster information website provides access to a broad range of emergency preparedness and response information. The Center also collaborates with the Navy National Medical Center, Suburban Hospital, Johns Hopkins Medicine, and NIH CC in the Bethesda Hospital Emergency Preparedness Partnership to provide backup communication systems and develop tools for patient tracking, information sharing and access, and responder training and to serve as a model for hospitals across the Nation. NIH also develops advanced information services and tools to assist emergency responders when disaster strikes. WISER (Wireless Information System for Emergency Responders) was developed for use during hazardous materials incidents and is available on the Internet or for downloading onto PDAs and PCs. Usage continues to grow, with more than 47,000 downloads onto PDAs in FY 2008. Radiation Event Medical Management (REMM) is a downloadable toolkit for use by health care providers during a mass casualty radiation event, with a version for mobile platforms released in FY 2008. Developed in collaboration with the HHS Office of Public Health Preparedness, REMM includes procedures for diagnosis and management of radiation contamination and exposure, guidance for use of radiation medical countermeasures, among other features to facilitate medical responses to radiation emergencies.

- For more information, see <http://disasterinfo.nlm.nih.gov>
- For more information, see <http://wiser.nlm.nih.gov>
- For more information, see <http://remm.nlm.nih.gov>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (NLM)

Partnerships for Environmental Public Health: NIH is developing a unified program referred to as "Partnerships for Environmental Public Health" (PEPH). PEPH will support activities to build new partnerships with community groups/stakeholders, develop and/or disseminate educational and outreach materials, enhance communication with partners (i.e., town meetings, forums on selected topics), evaluate (process and outcome evaluations) strategies to quantify public health impact, or engage community and researchers in Environmental Health Science research projects. The purpose of this program is to provide support for grantees already working in this area to enhance current grant activities within the scope of the peer-reviewed application and to encourage scientists with a traditional research focus to communicate/translate their research into materials or messages that are useful to other groups, such as the lay public, health care professionals, decisionmakers, or educators. Building partnerships and translating research to communities is an important component in promoting health and preventing exposures that may have adverse human health effects. By building environmental health and science literacy, community residents are better prepared and equipped to take personal and community action to reduce exposures. Partnerships between researchers and community groups foster trust and lead

to the identification of environmental health issues of concern to community residents, which may enhance the research results due to increased community participation.

- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NIEHS)

Outreach to the Scientific and Research Communities

AIDS Information Services: NIH manages the HHS-wide *AIDSinfo* service, which offers the latest federally approved information on HIV/AIDS clinical research, treatment and prevention, and medical practice guidelines that are developed by working groups under the auspices of the OAR Advisory Council. An *AIDSinfo* trans-agency steering group spans NIH, FDA, HRSA, and CDC. *InfoSIDA*, a Spanish-language version, features a customized home page and a search engine that locates Spanish-language resources within *AIDSinfo*. A new initiative to incorporate tens of thousands of abstracts from AIDS-related conferences held over the last decade into NIH's Web-based electronic information services also is underway, and testing for the first public release of the new data was conducted in FY 2009. In addition to providing information systems, NIH supports community outreach programs for underserved communities and special populations to promote improved access to HIV/AIDS information for health professionals, patients, the affected community, caregivers, and the general public. Emphasis is placed on supporting community-based organizations, libraries, faith-based organizations, and health departments to design and implement local programs that include information access topics related to information retrieval, skills development, Internet access, resource development, and document access, e.g., through collaboration with local public libraries. In FYs 2008-2009, NIH made 25 community outreach awards.

- For more information, see <http://aidsinfo.nih.gov>
- For more information, see <http://aidsinfo.nih.gov/infoSIDA/>
- For more information, see http://sis.nlm.nih.gov/outreach/hiv_outreach.html
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (I) (NLM)

NIH Consensus Development Program: This program, administered by the Office of Medical Applications of Research (OMAR) within the Office of the Director, NIH, was established in 1977 as a mechanism to assess, translate, and disseminate the results of biomedical research. Since its inception, OMAR has conducted more than 120 Consensus Development Conferences, and 30 State-of-the-Science (formerly "Technology Assessment") Conferences. The program generates evidence-based statements addressing controversial issues in medicine and public health that are useful and relevant for health care providers, policymakers, patients, researchers, and the general public. The conferences are structured around key questions, including questions on the efficacy, risks, and clinical applications of a technology, along with current gaps in knowledge to help formulate directions for future research. For every conference, a systematic evidence review is performed through a partnership with the Agency for Healthcare Research and Quality to serve as the foundation upon which the conference will build. Experts in the field provide additional input and insights through several days of oral presentations. The conferences also contain sessions for public input and discussion. A multidisciplinary, nonadvocacy, independent panel free from scientific or financial conflicts considers all of this information, and then writes a statement answering the posed conference questions. Consensus and state-of-the-science statements are disseminated widely after the conference to either impact clinical practice—when evidence strongly supports the use (or avoidance) of a particular intervention—or to direct future research—when important gaps in knowledge have been identified. Upcoming conferences in 2010 include: Enhancing Use and Quality of Colorectal Cancer Screening; Lactose Intolerance and Health; Vaginal Birth After Cesarean: New Insights; Preventing Alzheimer's Disease and Cognitive Decline; and Inhaled Nitric Oxide Therapy for Preterm Infants.

Health Communication and Information Campaigns and Clearinghouses

- For more information, see <http://consensus.nih.gov/>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) **(ODP/OMAR)**

Partners in Information Access for the Public Health Workforce (PH Partners): PH Partners, a 12-member public-private collaboration initiated by NIH, the Centers for Disease Control and Prevention, and the National Network of Libraries of Medicine assists the public health workforce to make effective use of electronic information sources. The Partners website, PHPartners.org, provides unified access to public health information resources produced by all members of the Partnership, as well as other reputable organizations. One of the most popular resources on the site is the Healthy People 2010 Information Access Project. In FY 2008, the website was expanded with more than 650 new links, and two new topic pages covering nutrition and workforce development were added.

- For more information, see <http://www.PHPartners.org>
- (I) **(NLM)**

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⁶⁴ The NIH National Resource Center is a partnership with support from NIA, the Eunice Kennedy Shriver NICHD, NIDCR, NIDDK, the NIH Office of Research on Women’s Health, and the HHS Office on Women’s Health.

⁶⁵ For more information, see <http://www.health.gov/communication/literacy/issuebrief/>.

⁶⁶ For more information, see <http://nces.ed.gov/naal>.

⁶⁷ For more information, see <http://www.nih.gov/icd/od/ocpl/resources/healthliteracyresearch.htm>.

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