

Summary of Research Activities by Key Approach and Resource

Technology Development

In July of 2002, a U.S. team of surgeons performed surgery on a patient by remote control 4,000 miles away in France. The surgeons were in New York, where they monitored the patient on the screen as they used tools connected to hi-tech sensors. The sensors turned the movement of the surgeon's hands into signals that sped across the Atlantic through fiber-optic lines to guide robots that operated on a 68-year-old woman in Strasbourg. The patient had no complications and was discharged 2 days later. The 54-minute procedure, dubbed "Operation Lindbergh" in honor of Charles Lindbergh's solo flight across the Atlantic, was the first of its kind. This technological milestone raises the possibility of remote robot surgery on wounded soldiers on battlefields, astronauts in space, and individuals in remote rural settings. Also, patients needing particularly difficult surgeries may have worldwide access to top surgeons without the need to travel.

Introduction

NIH support of technology development has triggered a revolution in the understanding of health and disease. A notable example is the Human Genome Project (jointly funded by NIH and the Department of Energy), which culminated in the sequencing of the human genome. Technology development, ranging from rapid DNA sequencing machines to complex computational tools to assemble the sequences, was critical to the successful sequencing of the human genome, as well as the genomes of numerous other organisms. This led to the development of a comprehensive map of human genetic variation and improved understanding of fundamental biological processes. This new knowledge continues to fuel the development of new clinical treatments, improving patient outcomes and quality of life.

During the past several decades, scientists have developed new technologies to create innovative animal models that closely mimic complex human disease. For example, through genetic engineering, a mouse model was created that mimics Alzheimer's disease. NIH-funded researchers are now using this model to study disease progression in the degenerating brain. This research is further enabled by the technological development of new imaging tools used to track the degeneration. This work provides an important step in the pathway to the discovery of new medications to treat Alzheimer's disease and perhaps change its course. Biotechnology and nanotechnology are examples of technology development. Biotechnology combines disciplines like genetics, molecular biology, biochemistry, embryology, and cell biology, which are in turn linked to practical disciplines like 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 refers broadly to a field whose unifying theme is the control of matter on the molecular level in scales smaller than one thousandth of a millimeter and the fabrication of devices within that size range. It is a highly multidisciplinary field, drawing from fields such as applied physics, materials science, supramolecular chemistry, and mechanical and electrical engineering.

Other examples of major breakthroughs spurred by NIH-supported technology development include:

- Progress in physical therapy for stroke survivors using wearable upper extremity robotic devices to mimic normal arm movements
- A new method of communication via a brain/computer interface for individuals with amyotrophic lateral

sclerosis and other neuromuscular disorders

- Improved epilepsy surgery outcomes using an integrated imaging system with precision-guided surgery to remove seizure-causing regions in the brain
- New diagnostic and imaging methods for the early detection of cancer and other diseases
- Innovative high-throughput methods for detecting and characterizing disease-causing alterations in genes and proteins
- Sensor technologies combining multiple analytical functions into self-contained, portable tabletop devices that can be used by non-specialists to rapidly detect and diagnose disease
- Cochlear implants to restore hearing to hearing-impaired individuals
- Left ventricular assist devices to aid the failing heart
- New treatments for abnormal heart rhythms such as atrial fibrillation

The interactions among technology development, basic research, and clinical application drive the engines of biomedical research, enabling scientists and clinicians to use sophisticated tools to unravel fundamental biological questions that underlie health and disease, as well as to develop new therapies considered inconceivable just a few years ago. For example, technological developments in electrodes, computers, and materials were critical in developing the scientific understanding of the nature of some abnormal heart rhythms. Those same basic technological developments are now critical for treatment of abnormal heart rhythms using advanced imaging and ablation techniques.

Interdisciplinary or team research offers one of the best opportunities to develop new technologies and refine current ones. A team approach 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 was originally developed in the context of communication research. In medicine, the technology 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 strong linkages among engineering, clinical medicine, physical science, computational science, and the biological sciences.

Scope of NIH Activity in Technology Development

To truly revolutionize medicine and improve human health, scientists need a more detailed understanding of the vast networks of molecules that make up cells and tissues, their interactions, and their regulation. Researchers also must have a more precise knowledge of the combination of molecular events leading to a given disease. In 2002, NIH recognized that a gap existed in the support of crosscutting technology development. In response to that need, 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. To capitalize on the completion of the human genome sequence and recent discoveries in molecular and cell biology, the research community needs wide access to technologies, databases, and other scientific resources that are more sensitive, robust, and easily adaptable to researchers’ individual needs. 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. The Roadmap was created to fulfill the need to apply crosscutting technology to numerous biomedical research and health challenges.

Technology development for a specific disease or organ system is supported by the relevant disease-specific NIH Institute. For example, NHLBI supports technology development to treat abnormal heart rhythms and stroke while NCI supports the development of technology to more effectively diagnose and treat cancer. In addition to the disease-specific Institutes, NIBIB and NCRR support broad areas of technology development and infrastructure. For example, NIBIB’s mission is to improve health by leading the development and acceleration of the translation of biomedical technologies. NIBIB supports interdisciplinary research aimed at developing fundamental or crosscutting technologies that can be translated into several biomedical applications. This work often is done in collaboration with a disease-specific Institute as the work moves closer to clinical application. Similarly, NCRR

provides laboratory scientists and clinical researchers with the research infrastructure and tools to develop technology to understand, detect, treat, and prevent a wide range of diseases.

Recognizing the potential benefits to human health to be realized from applying and advancing the field of bioengineering, the [Bioengineering Consortium](#) (BECON) was established at NIH in 1997. BECON is composed of senior-level representatives from each of the NIH Institutes as well as other Federal agencies. BECON's mission is to foster new basic understanding, collaboration, and transdisciplinary initiatives among the biological, medical, physical, engineering, and computational sciences—all important and necessary components in technology development.

NIH supports technology development through several complementary mechanisms, including:

- High-risk, innovative projects with very little preliminary indication of the likelihood of success but a potentially significant impact (e.g., R21 funding mechanism). These projects may 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. The Biomedical Technology Research Resources program creates these unique technologies, applies them to the most challenging problems in biology and medicine, and disseminates these capabilities into the broader research community. This program serves as an engine for translation of advances in the physical sciences into tools for biomedical and clinical research.
- Small business grants 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.

Summary of NIH Activities

Toward a New Era in Medicine

By 2030, just over 970 million people will be age 65 years or older worldwide. Medical advances will increase life expectancy and make acute diseases less frequent. However, chronic diseases and disabilities will have a major impact on health care in terms of both costs and patient management¹⁰. Health care in the future must be prepared to manage the challenges of an older population as well as continue to improve quality of life for younger individuals. Developments in technology will be central to the scientific advances that will lead to predictive, personalized, and preemptive medicine to equip our health care system to meet these challenges.

One example from past advances illustrates the potential of new technologies. A major breakthrough in the last 30 years, the cochlear implant, is an electronic device that gives individuals who are profoundly deaf or severely hard of hearing an opportunity to experience sounds. Although the device does not restore normal hearing, it does enable these individuals to understand and discern not only sounds in the environment but human speech as well. In the United States about 22,000 adults and nearly 15,000 children have received the implant. NIH has supported the initial development and continuing improvements of this technology over the past 30 years. According to scientists, profoundly deaf children who receive an implant at an early age develop language skills at a comparable

¹⁰ For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5206a2.htm>

rate to children with normal hearing. This device is allowing researchers to undertake large studies to determine how treatments such as the cochlear implant lead to better speech and language acquisition, academic performance, and economic outcomes for children with the implant. Results from these studies could lead to new recommendations for early intervention among infants who are profoundly deaf¹¹.

The research pipeline is replete with similar examples of NIH's commitment to technology development, its foresight in identifying emerging needs and emerging areas of investigation, and its ability to foster the development of technology that links basic research with clinical applications. Advances in research will continue to alter conventional medicine and lifestyle and NIH-supported technology development initiatives are central to improved understanding of scientific processes as well as improvements in health care. The following is an overview of technology development activities at NIH.

Gene Sequencing and Beyond

Mapping the human genome has created the opportunity to predict which individuals or groups may develop a disease or condition. To enter an era where personalized medicine is more readily available, in which specific genetic differences conferring susceptibility to disease can be easily determined and tailored therapies provided, researchers will need innovative sequencing technologies that are more efficient and cost-effective than current approaches. Relatively inexpensive sequencing devices would enable clinicians to tailor prevention, diagnosis, and treatment to each individual's unique genetic profile. To this end, NIH is awarding "\$1,000 Genome Grants" to develop breakthrough technologies that will enable an entire human-sized genome to be sequenced for \$1,000 or less. Currently, only analyses of ~ 500,000 Single Nucleotide Polymorphisms (SNPs) are being performed commercially at this cost; an individual's complete genome sequence (~ 3 billion base pairs) would offer vastly more information. Researchers will investigate use of nanotechnology, spectroscopy, and lab-on-chip approaches to find low-cost approaches to sequencing DNA. [Lab-on-chip](#) devices integrate multiple laboratory functions on a single microelectromechanical device of only millimeters to a few square centimeters in size.

Probing Proteins

Information from the Human Genome Project is now helping scientists as they begin to study proteins, the tiny powerhouses within cells responsible for cell function. Each protein is encoded with a specific sequence based on information found in genes but few tools have been available to examine protein structures and functions. A better understanding of protein activities could provide important information on why a disease develops. It also could lead to targeted drug therapies. 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. Many of the technologies conceptualized during PSI's first phase have been commercialized and are being used in laboratories. Some of the developments include:

- Miniaturization of samples needed to grow, purify, and crystallize proteins
- Robotic systems to handle samples and image crystals
- Enhanced software to analyze structural data and create higher resolution images
- More accurate screening processes to detect crystals suitable for imaging
- Improved systems for making proteins from machines instead of cells

These advances have reduced the cost, time, and space needed to carry out structural studies and have improved the generation and analysis of quality data¹². 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. Recently, PSI-funded scientists

¹¹ [Nicholas JG, Geers AE. *Eur Hear* 2006;27:286-98](#), PMID: 16672797

¹² For more information, see <http://www.nigms.nih.gov/News/Results/110606a.htm>

discovered a protein thought to be responsible for a lethal bacterial infection that affects the lungs of cystic fibrosis patients. Following this discovery, another set of researchers designed an experiment that provided important information on how the bacteria work. This collaborative effort could result in the development of a new drug to treat the infection.

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. NIH-supported researchers are also using mouse models whose brains contain genetically altered neurons to study how Alzheimer's and Parkinson's diseases mediate brain activity. In this research investigators activate or inhibit neurons using specific light frequencies. The work could be extended to clinical application by targeting neurons or cells involved in the disease process. In the case of Parkinson's disease, electrode-based deep-brain stimulation provides symptomatic relief but also can have side effects. Optical therapeutics that target diseased neurons could offer more precise therapy with fewer side effects¹³.

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, an NIH-funded team created a new optical microscope that permits scientists to see proteins that make up individual structures in a cell. The technique, known as photoactivated localization microscopy (PALM), may enable researchers to examine, for example, the proteins that control the organization and growth of HIV, the virus that causes AIDS. This information could be used to identify targets for drug development to halt viral replication.

Noninvasive molecular imaging using positron emission tomography (PET) and magnetic resonance imaging (MRI) is a fast developing area of research. By itself PET reveals information about such processes as metabolism or gene expression and is a key tool in basic cancer research as well as in providing clinical information for diagnosis and treatment of cancer patients. MRI provides information on anatomical structures. Two NIH-supported groups are developing imaging systems that combine PET and MRI. This research could lead to further understanding of how drugs disperse after administration; cardiac, central nervous system, and tumor cell metabolism; and mapping of neuroreceptors in small-animal brains. None of this is possible using current technology. A second group recently announced the first images of the human brain with a combined PET/MRI system. PET/MRI studies could allow clinicians to more definitively determine cognitive impairment and atrophy¹⁴.

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 or computed tomography (CT)—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

¹³ [Zhang F et al. *Nature* 2007;446:633-9](#), PMID: 17410168

¹⁴ [Judenhofer MS et al. *Radiology* 2007;244:807-14](#), PMID: 17709830

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.

As an emerging clinical tool, IGI shows great promise but is hindered by a number of factors¹⁵. An NIH-sponsored workshop noted that collaboration was one of the biggest hurdles facing the field. Interdisciplinary research and collaboration in the fields of biology, medicine, computer science, physics, and engineering will help create fast, reliable, and cost-effective IGIs.

Technological advancements require:

- More refined robotics technology for surgery and biopsies
- Expanded data integration
- Improvements in real-time modeling and three-dimensional visualization techniques
- Better approaches to image acquisition

Diagnostics and Point-of-Care Technology

Ideally, patients would have access to high-quality and consistent health care and treatment regardless of where they live. Realizing this vision necessitates the development of portable, reliable, and inexpensive equipment. To achieve this will also 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, or the transmission via the Internet of medical information, to communicate with other physicians or pathologists thousands of miles away. In Tucson, Arizona, for example, a breast health center provides same-day mammogram, biopsy, and diagnosis of breast cancer to women in rural locations using a pathology tool developed by NIH-funded engineers. By combining rapid tissue processing with telepathology and teleoncology, cancer diagnosis times have dropped to a matter of hours rather than a 1- to 2-week wait.

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 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 laboratory analyzer developed with NIH support that can identify specific bacteria responsible for urinary tract infections from a single drop of urine and do so in a matter of minutes rather than the 48 hours normally required in standard cultures.

Recent NIH-supported efforts in the design and microfabrication of electronic, optical, mechanical, and fluidic components for sensors and imaging devices have led to major advances in laboratory sample analysis. Several efforts target portable diagnostic platforms. One group has created a user-friendly miniaturized system that precisely measures levels of various antibodies, antigens, and nucleic acids found in saliva. The prototype is a low-cost disposable device that processes small amounts of saliva, amplifies its DNA, and detects the levels of DNA sequences of interest. Another group has developed a product to improve oral cancer detection. Created for dental office use, the handheld device emits a cone of light into the mouth that causes molecules within the cells to fluoresce. Normal oral tissue emits a pale green fluorescence while early oral tumor cells appear dark green or black.

Understanding the role that environment plays in the disease process requires accurate quantitative assessment. One novel NIH program aims to support development of technologies that make precise quantitative measurements of personal exposure to environmental chemical/biological agents, diet, physical activity, and psychosocial stress. Relatively inexpensive, lightweight, portable monitors and sensors such as wristbands, watches, or phones can be used to relay data from an individual to a central collective data bank.

¹⁵ From Final Report of the Image-Guided Interventions 2004 Workshop, May 13-14, 2004, Bethesda, Maryland..

NIH, along with the National Science Foundation, sponsored a workshop in 2006 to assess technological developments needed for advances in point-of-care testing and to identify clinical problems that could benefit from a point-of-care approach. As a result, NIH is supporting a program designed to create a national network of expertise to develop technologies that will address unmet clinical needs in global health, early detection of neurological emergencies (strokes), and detection of pathogens in emergency and disaster situations.

While some technologies have experienced widespread acceptance, several barriers must be overcome to make point-of-care diagnostics the norm. These include:

- Combining individual components into fully integrated systems that can handle all aspects of analysis
- Capturing data from these devices and transmitting it to clinical information systems
- Facilitating assessment of clinical opportunities in point-of-care testing to guide the development of emerging technologies
- Developing infrastructure to create multidisciplinary research collaborations that facilitate clinical testing early in the development process
- Validating results from point-of-care technologies
- Developing user-friendly devices
- Proving that point-of-care testing provides a clinical benefit over analysis at a central laboratory

Large-Scale Collaborative Activities

Multidisciplinary teams are essential to solving the complex problems that many emerging fields present. NIH-supported investigators in the promising field of tissue engineering and regenerative medicine, for instance, draw on the expertise of chemists, physicists, biologists, engineers, and computer scientists, among others. Coordinated efforts among these different groups are vital to continue progress made over the last two decades that has included fabrication of the first artificial organs. To make engineered tissue a viable clinical option, new computer programs must be designed to model the tissue in three dimensions. Novel approaches to fabrication and manufacturing are also needed for widespread use.

In an effort to develop new collaborations, NIH has implemented the Partnerships to Promote Innovation program. Examples of activities supported through this program include a cooperative research and development agreement, under which NIH and Siemens Medical Solutions will design new MRI technologies to diagnose and treat heart disease. Another agreement between NIH and the German National Research Center for the Environment will enable key genetic mouse models to be transferred to NIH investigators from the German Gene Trap Consortium.

The [Biomedical Technology Research Resources](#) (BTRRs) programs 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 imaging, informatics, synchrotrons, electron microscopy, proteomics and glycomics, optics, and lasers. Access to these technologies is critical to enabling research because they are frequently too advanced or expensive to be widely available. There are approximately 50 BTRRs located throughout the country that disseminate and promote the application of cutting-edge technologies they have 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, providing technological infrastructure, experimental and computational resources, and expertise.

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 (see also 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 initially was developed to allow neuroimagers to share data and tools, but the infrastructure is generic and therefore applicable to other disciplines. With the infrastructure in place and the lessons learned from the neurology projects, NIH has just released a set of program announcements to expand BIRN to support other large-scale, collaborative investigations.

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 into one that is predictive, personalized, preemptive, and participatory. These new tools and techniques are critical as the population ages and chronic, rather than acute, conditions become the norm.

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.

Notable Examples of NIH Activity

Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

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

COE = Supported through a congressionally mandated Center of Excellence program

GPRA Goal = Concerns progress tracked under the Government Performance and Results Act

Toward a New Era in Medicine

Pediatric Circulatory Support: Options for the circulatory support of pediatric patients younger than 5 years are currently limited to short-term extracorporeal devices, the use of which is often complicated by infection, bleeding, and blood clots. Recognizing the need for additional options, NIH established a program to facilitate the development of new circulatory support systems for infants and children with congenital or acquired cardiovascular diseases. The program supports five research groups developing a variety of devices for different pediatric applications. The common objective for the devices is to provide reliable circulatory support for infants and children while minimizing adverse effects.

- For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-HL-03-004.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NHLBI)

Cochlear Implants: One of the more groundbreaking biomedical achievements in the last 30 years has been the cochlear implant, an electronic device that provides a sense of sound to individuals who are profoundly deaf or severely hard of hearing. Cochlear implants process sounds from the environment and directly stimulate the auditory nerve, bypassing damaged portions of the inner ear. Nearly 100,000 individuals worldwide have been fitted with a cochlear implant. In the United States, roughly 22,000 adults and nearly 15,000 children have received one. Derived in part from NIH-funded research that dates back to the early 1970s and continues today, this

remarkable technology has enabled deaf and severely hard-of-hearing individuals to enjoy an enhanced quality of life. NIH-supported scientists showed that profoundly deaf children who receive a cochlear implant at a young age develop language skills at a rate comparable to children with normal hearing. NIH-supported scientists found that the benefits of the cochlear implant far outweigh its costs in children. Scientists can now study the large groups of children who were identified early for hearing loss and use this knowledge to document how treatments such as cochlear implants can lead to improved speech and language acquisition, academic performance, and economic outcomes for these children.

- [Nicholas JG, Geers AE. *Ear Hear* 2006;27:286-98](#), PMID: 16672797
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDCD)

Hearing Aids and Directional Microphones: Approximately 32.5 million American adults report some degree of hearing loss (NCHS/NHIS data for 2003). Although almost 95 percent of Americans with hearing loss could have their hearing treated with hearing aids, only about 20 percent of Americans with hearing loss have hearing aids and many who wear them are dissatisfied with their aids. Hearing in noisy environments is a major unsolved problem faced by hearing-aid users, and, of all available technologies, directional microphones currently show the most promise for addressing this problem. NIH-supported scientists have been studying the tiny fly *Ormia ochracea*, which has such sensitive directional hearing that it has inspired ideas for a new generation of hearing aids. The fly's ear structure, which permits ultrasensitive time coding and localization of sound, provides a model for scientists and engineers to use in developing new miniature directional microphones for hearing aids that can focus sound amplification on speech. To improve hearing aid technology so that users can better understand speech in a noisy background, NIH-supported scientists successfully completed a prototype of a low-power, highly directional microphone small enough to fit into a hearing aid. The use of improved directional microphones in hearing aids will improve the quality of life for individuals with hearing loss who depend on hearing aids to understand spoken language.

- [Miles RN, Hoy RR. *Audiol Neurootol* 2006;11:86-94](#), PMID: 16439831
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NIDCD) (GPRA Goal)

Gene Sequencing and Beyond

The Cancer Genome Atlas (TCGA): TCGA is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. The goal of TCGA is to develop a free, rapidly available, publicly accessible, comprehensive catalogue, or atlas, of the many genetic changes that occur in cancers, from chromosome rearrangements to DNA mutations to epigenetic changes—the chemical modifications of DNA that can turn genes on or off without altering the DNA sequence. The overarching goal of TCGA is to improve our ability to diagnose, treat, and prevent cancer.

- For more information, see <http://cancergenome.nih.gov/index.asp>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Genomics*.
- (E/I) (NCI, NHGRI)

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. The initial 4-year pilot phase has just been completed, and the consortium has published a series of papers describing an intricate network in which genes and other regulatory mechanisms interact in complex ways. Other insights include the discovery that the majority of DNA in the human genome is transcribed into functional molecules, called RNA, and that these transcripts extensively overlap one another. These findings challenge long-held beliefs that the genome has small sets of

genes and vast amounts of “junk” or untranscribed DNA. Until now, most studies have concentrated on the functional elements of specific genes, and have not provided information about functional elements in the vast majority of the genome that does not contain genes. ENCODE's exciting discoveries may well reshape the way scientists think about the genome and pave the way for more effective approaches to both understanding and improving human health.

- [The ENCODE Project Consortium, et al. *Nature* 2007;447:799-816](#), PMID: 17571346
- For more information, see <http://www.genome.gov/10005107>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHGRI)

Genome Technology and the \$1,000 and \$100,000 Genome Initiatives: DNA sequencing spells out the order in which our chemical building blocks are arranged, making DNA sequencing a powerful resource for biomedical research. Although DNA sequencing costs have dropped by more than three orders of magnitude since the start of the Human Genome Project, sequencing an individual's complete genome for medical purposes is still prohibitively expensive. Developing technology to make whole-genome sequencing more affordable would enable the sequencing of individual genomes to become part of routine medical care. The Genome Technology program supports research to develop new methods, technologies, and instruments to rapidly and at low cost:

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

Additionally, NHGRI supports two types of sequencing grants: (1) “Near-Term Development for Genome Sequencing” grants support research aimed at sequencing a human-sized genome at 100 times lower cost than is possible today (\$100,000) and (2) “Revolutionary Genome Sequencing Technologies” grants aim to develop breakthrough technologies that will enable a human-sized genome to be sequenced for \$1,000 or less. Currently, only analyses of ~ 500,000 Single Nucleotide Polymorphisms (SNPs) are being performed commercially at this cost; an individual's complete genome sequence (~ 3 billion base pairs) would offer vastly more information.

- For more information, see <http://www.genome.gov/10000368>
- For more information, see <http://www.genome.gov/19518500>
- This example also appears in Chapter 3: *Genomics*.
- (E) (NHGRI)

Large-Scale Sequencing Program: NIH's Large-scale Sequencing Program funds three major research centers in the United States to conduct genetic sequencing. During and since the completion of the Human Genome Project, NIH-funded centers have used their industrial-scale enterprises to improve DNA sequencing methods, thereby substantially decreasing costs and increasing capacity. For many years, the Program has achieved twofold decreases in cost approximately every 20 months. One of the main projects now under way is the sequencing of the genomes of other primates, such as orangutan, baboon, gibbon, and marmoset (in addition to chimpanzee and macaque, which are complete). By comparing the human genome to that of other primates, researchers can find important information about both health and abilities that are uniquely human and those shared with other species. The Program also supports the genomic sequencing of human pathogens (organisms that cause disease in humans) and their vectors, the organisms that carry those pathogens. Also, many mammals are being sequenced to identify elements that are functionally important to human biology. These studies will undoubtedly unveil new biological insights to increase our understanding of how the human genome works.

- [Rhesus Macaque Genome Sequencing and Analysis Consortium, et al. *Science* 2007; 316:222-34](#), PMID: 17431167
- For more information, see <http://www.genome.gov/10001691>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Sciences*.

- (E) (NHGRI)

Population Genomics, GAIN, and GEI: In February 2006, the U.S. Department of Health and Human Services announced the creation of two related groundbreaking initiatives in which NIH is playing a leading role. The Genetic Association Information Network (GAIN) and the Genes, Environment, and Health Initiative (GEI) will accelerate research on the causes of common diseases. GAIN is a public-private partnership among NIH, Foundation for the NIH, Pfizer, Affymetrix, Perlegen, Broad Institute, and Abbott. GEI is a trans-NIH effort combining comprehensive genetic analysis and environmental technology development to understand the causes of common diseases. Both GAIN and GEI are powered by completion of the “HapMap,” a detailed map of the 0.1 percent variation in the spelling of our DNA that is responsible for individual predispositions for health and disease. Data from GAIN will narrow the hunt for genes involved in six common diseases. In June 2007, the first GAIN dataset, on attention deficit hyperactivity disorder, was released. GEI will provide data for another approximately 15 disorders, and will develop enhanced technologies and tools to measure environmental toxins, dietary intake, and physical activity, as well as an individual's biological response to those influences.

- For more information, see <http://www.genome.gov/19518664>, <http://www.genome.gov/19518663>
- For more information, see <http://genesandenvironment.nih.gov/>, <http://www.genome.gov/11511175>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E/I) (NHGRI)

Probing Proteins

NIGMS/NCI Collaborative Access Team (GM/CA-CAT): Structural biology is a field in which scientists learn about molecules by determining their three-dimensional structures in atom-by-atom detail. Enormous 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 section of the synchrotron at Argonne National Laboratory (the Advanced Photon Source). The new section includes three stations (beamlines) that scientists from across the United States will be able to use to determine the detailed, three-dimensional structures of molecules. This sort of research is important to understanding basic biological processes and designing drugs. The facility was to be in full operation in the last quarter of 2007.

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

Clinical Proteomic Technologies Initiative for Cancer: The completion of the Human Genome Project in 2003 has been a major catalyst for proteomics research and NIH has taken a leading role in facilitating the translation of proteomics from research to clinical application through its Clinical Proteomic Technologies Initiative for Cancer. The overall objective of this Initiative is to build the foundation of technologies (assessment, optimization, and development), data, reagents and reference materials, computational analysis tools, and infrastructure needed to systematically advance our understanding of protein biology in cancer and accelerate discovery research and clinical applications.

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

Protein Structure Initiative: 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 can also greatly advance the design of medicines to treat a wide range of diseases. Recognizing this, NIGMS established the Protein Structure Initiative (PSI) in 2000. This multimillion dollar initiative involves hundreds of scientists across the Nation and is a collaborative effort between the Federal government, universities, and industries. Already, members of the PSI have determined thousands of structures and have developed new

technologies that improve the speed and ease of determining molecular structures. In addition to benefiting the PSI team, this work has accelerated research in other fields.

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

Membrane Protein Production and Structure Determination: The NIH Roadmap on Structural Biology seeks to develop innovative approaches and technologies for rapidly producing membrane proteins—the proteins tightly wedged within the lining of our cells. These protein samples can then be used to determine the proteins' underlying structures which will help researchers clarify the role of proteins in health and disease. Scientists currently have enormous difficulty pulling membrane proteins from cells in a condition suitable for functional and structural studies. Although these challenging proteins account for about 30 percent of all cellular proteins and are targets of 60-70 percent of known drugs, only about 100 structures of membrane proteins have been identified. In contrast, over 20,000 soluble protein structures have been determined. With the development of efficient protein-producing methods, researchers will be able to study and understand how membrane proteins function and interact with microbes, viruses, other cells, and drugs. By shifting the emphasis from hypothesis-driven research to technology development, the NIH Roadmap on Structural Biology has significantly impacted the membrane protein community. It has initiated collaborations among chemists, cell biologists, biophysicists, modelers, and physicists. Ultimately, the research will expand our knowledge of membrane protein structures, which may lead to improvements in drug design.

- For more information, see <http://nihroadmap.nih.gov/structuralbiology/>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-003.html>
- (E) (Roadmap—all ICs participate)

Insights From Animal Models

Tools to Reveal the Mechanisms Governing Behavior: Newly acquired but rapidly evolving tools and techniques that monitor or probe discrete brain systems have allowed NIH-supported researchers to begin filling in the information gap between molecular or cellular events and behavioral outcomes. A notable preclinical example of this trend is the development of a genetically engineered method to turn the electrical impulses of brain cells on and off with pulses of light, in synch with the split-second pace of real-time neuronal activity. The novel technique borrows genes from light-responsive algae and bacteria to unravel the intricate workings of brain circuits with extreme precision. This powerful new tool could be used to assess the role of neuronal activity in regulating normal behavior and disease processes. On the clinical side, an array of brain imaging devices has produced much information on how neural circuits develop and process information under normal conditions, and how they become impaired by a disease-like addiction. These advances have led to the fertile concept that the transition from abuse to addiction is not a switch but a gradual degradation of the ability of different circuits to “talk” to each other as they attempt to compensate for their deficiencies. Interestingly, these studies are also showing significant overlap in the circuits involved in drug abuse and the circuits underlying compulsive overeating and obesity. Moreover, in preclinical studies, compounds that interfere with food consumption in animal models of compulsive eating also interfere with drug administration.

- For more information, see <http://www.nimh.nih.gov/press/lightswitchneurons.cfm>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIDA, NIMH)

The Knockout Mouse Project (KOMP): The NIH Knockout Mouse Project (KOMP) is an NIH-wide effort to create a publicly available resource of knockout mouse mutations that can be used to study human disease. Knockout mice are strains of mice in which specific genes have been completely disrupted, or knocked out. By studying these mice, researchers can evaluate the effect of this systematic disruption of different genes on physiology and

development. Understanding the effects of gene disruption in mice will provide powerful tools to develop better models of inherited human disease. NIH has awarded 5-year cooperative agreements for the creation of knockout mice lines to Regeneron Pharmaceuticals Inc. to a collaborative team from Children's Hospital Oakland Research Institute, and to the Wellcome Trust Sanger Institute in England. NIH has also recently awarded \$4.8 million to the University of California, Davis, and the Children's Hospital Oakland Research Institute to establish and support a repository for the KOMP. The repository will enable many more researchers to have access to the knockout mice and will ensure product quality for the 8,500 types of knockout mice currently available.

- [Austin CP, et al. *Nat Genet* 2004;36:921-4](#), PMID: 15340423
- For more information, see www.komp.org
- This example also appears in Chapter 3: *Genomics*.
- (E/I) (NHGRI)

Multimodal PET and MRI Imaging Instrumentation: Investigators are developing a small animal PET/MRI system to study diseases such as cancer using animal models. This project will exploit the strengths of two widely used medical imaging modalities—positron emission tomography (PET) and magnetic resonance imaging (MRI). PET is a highly sensitive nuclear medicine imaging modality but requires radionucleotides and has poor spatial resolution. On the other hand, MRI has poor sensitivity but provides high spatial resolution and does not require radionucleotides. One expected application of the small animal PET/MRI system would be to develop imaging biomarkers for cancer. These biomarkers could provide new ways to monitor and test novel therapeutics, which may improve health care for cancer patients.

- [Catana C, et al. *J Nucl Med* 2006;47:1968-76](#), PMID: 17138739
- For more information, see <http://atlasserv.caltech.edu/~petmri/>
- (E) (NIBIB)

Imaging Biological Systems

The Cancer Imaging Program (CIP): The mission of CIP is to promote and support cancer-related basic, translational, and clinical research in imaging sciences. CIP initiatives include (a) development and delivery of image-dependent interventions for cancer and precancer, (b) standardized models for the design of clinical trials using imaging, (c) development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput screening, and (d) development of imaging methods to detect, treat, and monitor response to therapy.

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

Imaging Initiative From Molecules to Cells: Much human suffering is caused by the breakdown of the intricate and highly dynamic organization of the body at every level, starting with the structure of macromolecules such as proteins, progressing through ensembles of proteins that make molecular machines, to the sets of these machines that form organelles (mini-organs within cells), right up through cells and tissues. To make progress in fighting these diseases, we need to make progress in learning exactly how a pathogen, cancer cell, or faulty gene disorganizes living matter. The time is now ripe to turn the powerful new imaging approaches developed in physics and biophysics laboratories to the imaging of living material in health and disease, because then we can see exactly how things work and what goes wrong. IC intramural program leaders have collaboratively developed a strategic plan for trans-NIH efforts to realize the full potential of these powerful technologies for biomedical research. All of the NIH Institutes will play a role in moving forward on this plan, with leadership from the NIBIB, NICHD, and NCI.

- (I) (NIBIB, NCI, NICHD)

Molecular Imaging of G-Protein Coupled Receptors for Drug Development: What do over 50 percent of all therapeutic drugs have in common? They act on a specific type of receptor on the surface of cells known as the G-protein coupled receptor (GPCR). GPCRs form a large family of membrane-bound proteins containing seven transmembrane helices connecting an extracellular receptor site to an intracellular G-protein binding site. This transmembrane nature provides extracellular control over important intracellular functions. To date, all of the drugs that target GPCRs have been developed using screening approaches. These approaches have been effective but their cumbersome and expensive nature severely limits widespread development of novel GPCR-targeted drugs for cancer, heart disease, obesity, and many other illnesses. Novel “structure-based” methods can overcome these problems and have been very successful with HIV protease inhibitors. However, structure-based drug design methods have not been possible with GPCRs because of the complexity of the structure and the fact that it sits within the cell membrane. NIH-funded researchers are developing and extending novel “solid-state” NMR technology to design new approaches that can obtain “atomic resolution” three-dimensional structures of GPCRs in their natural environment of the cell membrane. This new approach to drug design may substantially increase the rate of development of specific GPCR-targeted drugs.

- [Park SH, et al. *J Am Chem Soc* 2006;128:7402-3](#), PMID: 16756269
- [Nezvorov AA, et al. *J Biomol NMR* 2007;37:113-6](#), PMID: 17216304
- For more information, see <http://nmrresource.ucsd.edu/facility/index.html>
- For more information, see <http://www.nibib.nih.gov/Research/ResourceCenters/Listname/Opella>
- (E) (NIBIB)

New Light Microscope: By blending emerging advances in physics and microbiology, NIH researchers developed a new light microscope that allows scientists for the first time to visualize and determine how proteins are arranged and compose individual structures within a cell. Known as photoactivated localization microscopy, or PALM, the new technique enables researchers to better view cell structures and understand the complexity of proteins, the cells' building blocks. For example, using PALM, researchers could study several cellular subsystems, including those that provide energy for the cell's activities. In addition, researchers could visualize the distribution of the proteins involved in the assembly and budding of the AIDS virus from a host cell, literally giving scientists new insights into targets to stop viral replication.

- [Betzig E et al. *Science* 2006;313:1642-5](#), PMID: 16902090
- For more information, see http://www.nichd.nih.gov/news/releases/microscope_view_protein.cfm
- (I) (NICHD)

Visualizing Transcription of Genes in Living Cells: Most genes serve one main purpose: as recipes for the body's proteins. The first step in using genes to produce proteins is called transcription. Although scientists think they know how transcription works, it has not been well studied in real-time in living cells. Now, NIH-supported researchers have developed fluorescent dyes and new techniques in microscopy that will enable them to watch transcription from individual genes. Faulty gene transcription can lead to cancer, so a detailed understanding of the process may lead to new ways to treat disease.

- [Yao J, et al. *Nature* 2006;442:1050-3](#), PMID: 16929308
- For more information, see <http://www.nature.com/nature/journal/v442/n7106/extref/nature05025-s3.mov>
- (E) (NIGMS)

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 are particularly important in light of the shifting trend in medicine toward a model of early, presymptomatic detection of disease. The need to support research and development in this area has been

identified at multiple workshops sponsored by NIH and other Federal agencies. In response, in August 2006, NIH issued a request for applications to support the first phase of a two-phase project that will deliver high-impact IGIs. Multidisciplinary collaborations and partnerships with industry were encouraged, with the goal of developing multipotential technologies with high clinical impact applicable across a range of diseases and disorders.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-06-003.html>
- (E) (NIBIB, NCI) (GPRA Goal)

Diagnosics and Point-of-Care Technologies

Diabetes Research in Children Network (DirecNet): The risk of hypoglycemia is now the main obstacle to successfully managing type 1 diabetes mellitus (T1DM) in children of all ages. Severe hypoglycemia can lead to seizures or unconsciousness. In 2001, NIH established DirecNet to assess the accuracy and efficacy of continuous glucose monitoring devices, evaluate the effectiveness of the devices as tools to help control blood sugar levels, and determine the incidence of hypoglycemia. DirecNet also focuses on possible changes in neurocognitive function in children with T1DM who have frequent bouts of hypoglycemia. The network was recently renewed to use new tools to evaluate factors and mechanisms contributing to hypoglycemia, such as exercise and diet. The goal is to continue to improve management of T1DM and prevent hypoglycemia by “closing the loop” between measuring glucose levels and delivering insulin.

- For more information, see <http://www.nichd.nih.gov/research/supported/directnet.cfm>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-06-020.html>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NICHD, NIDDK, NINDS)

Advances in Oral Cancer Detection: The first product of a current NIH-funded research project to integrate new technologies into a reliable clinical protocol to improve oral cancer detection and survival has reached the market. Researchers report success using a customized optical device that allows dentists to visualize in a completely new way whether a patient might have a developing oral cancer. The simple, handheld device emits a cone of light into the mouth that excites molecules within our cells, causing them to absorb the light energy and re-emit it as visible fluorescence. Remove the light, and the fluorescence disappears. Changes in the natural fluorescence of healthy tissue can indicate light-scattering changes caused by developing tumor cells. Health care providers shine a light onto a suspicious sore in the mouth, look through an attached eyepiece, and check for changes in color. Normal oral tissue emits a pale green fluorescence, while early tumor cells appear dark green to black. The instrument is an effective screening adjunct and is useful for helping surgeons determine how far to extend the surgical borders when removing tissue for biopsies.

- For more information, see <http://clincancerres.aacrjournals.org/cgi/content/full/12/22/6716>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDCR)

Salivary Diagnostics: NIH stands at the forefront of efforts to develop salivary diagnostics, the use of saliva as a robust, sensitive, reliable, low-cost, user-friendly “point of care” mechanism for early disease diagnosis, monitoring drug levels, and detecting environmental insults. Salivary tests can be performed on the spot and require no painful needle sticks. A number of grantees are currently working to develop a tiny automated machine that can precisely measure levels of the various antibodies, antigens, and nucleic acids present in saliva. Recently, the promise of salivary diagnostics moved closer to becoming technologically feasible with the fabrication of the first disposable, low-cost miniaturized diagnostic platform to process small amounts of saliva, amplify its DNA, and detect the levels of DNA sequences of interest. Once development of a similarly robust sample preparation process is complete, the cassette will offer the first fully integrated, highly flexible platform for multiple analysis paths.

- [Wang J, et al. *Lab Chip* 2006;6:46-53](#), PMID: 16372068

- (E) (NIDCR)

New Genetics Tools Shed Light on Addiction: NIH-supported research is taking full advantage of the massive databases and rapid technologies now available to study how genetic variations influence disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms and the genetic predispositions underlying diseases like addiction. 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). A next-generation “neurochip” is being developed with 24,000 gene variants related to substance use and other psychiatric disorders. Applying this tool to addiction and other brain disorders will advance our understanding of not only vulnerability to addiction and its frequent comorbidities, but also ways to target treatments based on a patient's genetic profile (i.e., a “pharmacogenetic” approach). To complement these efforts, NIH is investing heavily in the emerging 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. A focus on gene by environment interactions has recently been expanded to incorporate developmental processes, now known to also affect the outcome of these interactions. The resulting Genes, Environment, and Development Initiative (GEDI) seeks to investigate how interactions among these factors contribute to the etiology of substance abuse and related phenotypes in humans.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/rfa-da-07-012.html>
- For more information, see <http://nihroadmap.nih.gov/roadmap15update.asp>
- This example also appears in Chapter 3: *Genomics* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NIDA, NCI, NIAAA, NIMH) (GPRA Goal)

Exposure Biology Program of the GEI: As a major partner in the Genes, Environment, and Health Initiative within NIH, NIEHS has especially focused on the Exposure Biology/Exposure Measurement dimension of this initiative, through which we will improve the technologies for detection and measurement of the actual exposures sustained by human or other organisms that are currently often weak and imprecise. This is in contrast to the robust tools employed in the fields of genetics and genomics. Personalized measures of environmental exposure must be developed that are equivalent to the ability to measure genetic variability between individuals. The increasing sophistication of our understanding of the biological pathways involved in host response to a given exposure points the way toward the use of that knowledge to develop improved methods for detecting and measuring environmental exposures. Needed are relatively inexpensive, highly portable monitors—a wristband, watch, phone, or lightweight tote for example - that could accurately collect and retain large amounts of data on exposures and to some degree process that data into useful form. Recent advances in environmental and biological sensors suggest that the technologies are at hand, or can be readily engineered to provide precise measure of chemical and biological hazards at the point of contact and/or to characterize the biological fingerprint left by a class of environmental stressors. The value of these technologies would far exceed even the ingenuity required to create them, in enabling researchers to detect associations between environmental exposures and disease.

- For more information, see <http://www.gei.nih.gov/exposurebiology/index.asp>
- (E) (NIEHS) (GPRA Goal)

Alcohol Biosensors Program: This Advanced Research Program, modeled on the U.S. Department of Defense's DARPA (Defense Advanced Research Projects Agency) program, was developed by NIH to generate a technical solution to address the need for continuous measurement of alcohol concentrations over time in clinical and basic research on alcohol use disorders. NIH awarded five research and development contracts for alcohol biosensor development. Each research group employed a different technological approach for alcohol measurement, and all have made substantial progress in engineering commercially viable alcohol biosensors, some of which will likely make their way to market in the next few years.

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

Point-of-Care Research Network: The need to improve the quality and accessibility of care while reducing costs is a significant challenge currently faced by the Nation's health care system. Adding to this challenge is the need to reduce health disparities and provide care for an aging population. Significant improvements in health care delivery can be achieved through the development of point-of-care systems that can be integrated into the health care delivery system through information and communications technologies. A major challenge in this effort is to evaluate the clinical feasibility of integrated technology in sensors, microsystems, imaging, and informatics. To address this challenge, NIH is establishing a Research Network that will develop integrated systems that address unmet clinical needs in point-of-care testing. This will be accomplished through the creation of multidisciplinary partnerships that will interact across the network to enable broad coverage of clinical and technological issues in point-of-care testing.

- For more information, see <http://www.nibib.nih.gov/NewsEvents/SympReports/2006Apr11>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-06-002.html>
- (E) (NIBIB)

Newborn Screening: Screening and treating newborns for phenylketonuria (PKU) and hypothyroidism have virtually eliminated these conditions as a cause of mental retardation in the United States. A new, trans-NIH collaborative effort will build on this success to develop a new generation of microchips and related technologies that should enable screening programs across the Nation to rapidly test newborns for hundreds of genetic conditions in a single test using one drop of an infant's blood. Complementing the technology development is an initiative to stimulate development of new treatments for such conditions as short chain Acyl CoA dehydrogenase deficiency (SCAD), tyrosinemia, and the genetic causes of hearing loss with the promise of significantly reducing the lifelong health burden of these and other conditions.

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

Wireless Information System for Emergency Responders (WISER®): WISER is a system designed to assist first responders in hazardous material incidents by providing a wide range of information on hazardous substances, including substance identification support, physical characteristics, human health information, and containment and suppression advice. In 2007, several important features were added to WISER, including radiological support with data for over 20 isotope substances and tools/reference materials for radiological incidents. A new partnership with the U.S. Department of Transportation (DoT) enabled integration of the DoT's Emergency Response Guidebook (ERG) 2004 with WISER and the development of a stand-alone ERG 2004 Mobile version. Widely used by first responders, WISER is available for downloading onto PDAs and Windows-based platforms or for browsing on the Web.

- For more information, see <http://wiser.nlm.nih.gov>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (I) (NLM)

Genes, Environment, and Health Initiative, Exposure Biology Program: This trans-NIH initiative supports the development of environmental sensors for measurement of chemicals, dietary intake, physical activity, psychosocial stressors, and addictive substances and of "fingerprints" (markers) of biological response to exposures to these environmental factors. These new methods will ultimately be used to monitor environmental exposures that interact with genetic variations that influence health and disease. In addition, a workshop on measuring psychosocial stress and the social environment is planned for early FY 2008.

- For more information, see <http://www.gei.nih.gov/exposurebiology/>
- (E) (OD)

Large-Scale Collaborative Activities

Partnerships to Promote Innovation: NIH has implemented new collaborations with electronics and pharmaceutical industry leaders and with the German government to develop innovative technologies and their application to biomedical research. A Cooperative Research and Development Agreement (CRADA) between NIH and Siemens Medical Solutions has been adopted to promote the design of new magnetic resonance imaging methods for the diagnosis and treatment of heart disease. A material transfer agreement between NIH and the German National Research Center for the Environment is being negotiated to facilitate the transfer of important mouse genetic models from the German Gene Trap Consortium mouse distribution facility to NIH investigators. Additionally, a Materials-CRADA has been negotiated between NIH and Merck & Co. to facilitate transfer of proprietary Merck biologics and compounds for internal NIH research and development, with the specific aims of reducing transaction costs and getting necessary research materials into the hands of NIH investigators quickly and efficiently.

- [Kellman P, et al. *Magn Reson Med* 2005;53:194-200](#), PMID: 15690519
- For more information, see <http://tikus.gsf.de>
- (I) (NHLBI)

Innovative Technologies for Engineering Small Blood Vessels: NIH has initiated a program of basic research studies to enlighten future development of replacements for damaged or diseased small blood vessels. Thousands of patients each year could benefit from small blood vessel substitutes (e.g., to bypass coronary artery or peripheral vascular occlusions or to establish arteriovenous shunts for hemodialysis), but currently available replacement grafts have a high failure rate. Recent advances in materials science, bioengineering, and tissue engineering, as well as the availability of better computational tools, are providing opportunities for the development of replacement blood vessels with properties that closely match those of natural blood vessels.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHLBI)

The NCI Alliance for Nanotechnology in Cancer: This is a comprehensive, systematized initiative encompassing the public and private sectors, designed to accelerate the application of the best capabilities of nanotechnology to cancer. The program supports research on novel nanodevices that may detect and pinpoint the location of cancer at its earliest stages, deliver anticancer drugs specifically to malignant cells, and determine in real time whether these drugs are effective at killing malignant cells. Nanotechnology will likely change the very foundations of cancer diagnosis, treatment, and prevention.

- For more information, visit <http://nano.cancer.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research*.
- (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 easily and widely shared 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 utilizing the capabilities of the emerging

national cyberinfrastructure. The project includes a Coordinating Center at the University of California, San Diego, which serves the critical task of developing, deploying, and maintaining key infrastructure components, including high-bandwidth connectivity, grid-based security, file management and computational services, techniques to federate databases, and shared visualization and analysis environments.

- For more information, see <http://www.nbirn.net/>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NCRR)

Biomedical Technology Research Resources (BTRRs): The BTRRs 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 Resources and through intensive collaborations with other leading laboratories. The BTRRs are used annually by nearly 5,000 scientists from across the United States and beyond, representing over \$700 million of NIH funding for 22 institutes and centers. 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: *Molecular Biology and Basic Sciences*.
 - (E) (NCRR)

Glycomics Technology Development, Basic Research, and Translation Into the Clinic: Complex carbohydrates are ubiquitous, 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 are thus critical for basic and clinical research across the spectrum of health and disease, but widely regarded as among 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 Resources are developing and sharing 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/biomedical_technology/biomedical_technology_research_resources/technology_for_systems_biology/glycomics.asp

- For more information, see <http://www.functionalglycomics.org/static/index.shtml>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NCR, NCI, NHLBI, NIGMS, NINDS)

Enabling Technologies in Tissue Engineering and Regenerative Medicine: Tissue engineering and regenerative medicine are interdisciplinary fields in which basic science aimed at understanding the cellular machinery combines with computational and engineering processes to control and direct the aggregate behavior of cells to form tissues and organs. While much progress has been made over the 20 or so years since the field first started, key technologies such as technology to rapidly expand, direct (along a specific cell line path), preserve, and track cells are not yet in place to accelerate development on all fronts. A program announcement sponsored by NIH, the National Science Foundation, and the National Institute of Standards and Technology was issued in 2006 and is focused on developing new infrastructural tools for the field. The funding opportunity will be open through FY 2008 in order to attract the best and most innovative ideas and research plans to advance the field.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-06-504.html>
- (E) (NIBIB, NHLBI, NIAMS, NICHD, NIDCD, NIDCR)

National Centers for Biomedical Computing (NCBCs): The NIH Roadmap Bioinformatics and Computational Biology initiative provides a networked national effort to build computational tools and infrastructure for biomedical computing. The centers are devoted to all facets of biomedical computing, from basic research in computational science to providing the tools and resources that biomedical, clinical, and behavioral researchers need to do their work. The seven centers currently supported by the NIH Roadmap have made substantial progress in software development, data resources, and scientific ontologies. These advances are currently being used by the research community for studying a broad range of biological problems including cerebral palsy, autism, diabetes, asthma, Alzheimer's disease, Huntington's disease, schizophrenia, bipolar disorder, HIV/AIDS, and prostate cancer. The long-term goal of the initiative is to create a national software engineering system that will enable biomedical and clinical researchers to share and analyze data using a common set of software tools.

- For more information, see <http://nihroadmap.nih.gov/bioinformatics/>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (Roadmap—all ICs participate)

Transforming Health Care

New Medical Adhesive Boasts Unique Wet-Dry Abilities: One day, tissue engineering will make it possible to regenerate lost facial components. Until then, victims of massive craniofacial trauma or extensive surgeries due to cancer often must depend on maxillofacial prosthetics to provide the form and function needed to resume their day-to-day lives. Current adhesives are not always retentive over long periods or changing conditions. The loss of retention can result in visible margins or even dislodgement of the prosthesis. Now NIH-supported scientists report they have merged two of nature's most elegant strategies for wet and dry adhesion. As reported in *Nature*, the scientists designed a synthetic material that starts with the dry adhesive properties of the gecko lizard and supplements it with the underwater adhesive properties of a mussel. The hybrid material, which they call a geckel nanoadhesive, proved in initial testing to be adherent under dry and wet conditions, and also adhered much longer under both extremes than previous gecko-based synthetic adhesives, a major issue in this area of research. According to the authors, their findings mark the first time that two polar opposite adhesion strategies in nature have been merged into a man-made reversible adhesive. It is envisioned that the new adhesive will be used for many medical applications including enhancing the retention of oral/maxillofacial prosthetics.

- [Lee H, et al. *Nature* 2007;448:338-41](#), PMID: 1763766
- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/NRY2007/PR07182007.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 2: *Life Stages, Human Development*,

and Rehabilitation.

- (E) (NIDCR)

Suture Developed Using DNA Technology: Supported by an SBIR award, scientists at Tepha, Inc., have developed a new, bioabsorbable surgical suture that is stronger, more flexible, and capable of retaining its strength longer than existing absorbable sutures. The scientists created the suture material in a new way, by genetically engineering bacteria to produce it for them. In February 2007, the FDA approved Tepha's ability to market the sutures. The company hopes that, in the future, the same material will be used for other medical devices, like surgical meshes for hernia repair, artificial heart valves, absorbable stents, and devices to repair and replace ligaments and tendons.

- For more information, see <http://www.tepha.com/publications/media.htm?ident=21>
- (E) (NIGMS)

Neural Prosthesis Program: 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. The NINDS Neural Prosthesis program pioneered the development of this technology beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants for the hearing impaired, respiratory and hand grasp devices for people with spinal cord injuries, and deep brain stimulation for patients with Parkinson's disease, among other contributions. Current work aims to restore standing and voluntary bowel and bladder control after spinal cord injury, to allow paralyzed persons to control devices directly from their brains, and to control seizures. Ongoing research also seeks to improve cochlear implants and to advance 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 NIH Institutes, which coordinate their efforts with programs now under way in the Department of Veterans Affairs and DoD.

- 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, NIBIB, NIDCD, NICHD, NEI)

The Cancer Biomedical Informatics Grid™ (caBIG): The caBIG initiative has been launched to accelerate research discoveries and improve patient outcomes by linking researchers, physicians, and patients throughout the cancer community. caBIG™ completed its 3-year pilot project in March 2007. This date represents a new phase of evolution, as NIH is committed to bringing caBIG™ into an enterprise model that can be extended and sustained across a broader community.

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

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 on 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 2006 and 2007 the SIG program funded a total of 264 grants for \$95.2 million; the HEI funded a total of 39 awards for \$55.9 million.

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

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. For example, a dietary supplement that boasts “500 mg of Vitamin C from rosehips per tablet” on its label should be expected to contain both 500 mg of Vitamin C and rosehips. 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 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. An external panel of experts recently reviewed the Program and found that it had substantially raised the awareness of the need for better quality-control measures within the dietary supplement community and provided research funding crucial for development, validation, and dissemination of reference materials and analytical methods.

- For more information, see http://dietary-supplements.info.nih.gov/Research/Analytical_Methods_and_Reference_Materials_Program.aspx
- (E) (ODS)

Evidence-Based Review Program: In FY 2001, congressional appropriations report language included text asking that NIH review the current scientific evidence on the efficacy and safety of dietary supplements and identify research needs. In response, NIH established 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 institutes and centers 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. Currently, NIH is sponsoring an evidence report on *Effectiveness and Safety of Vitamin D* that will be used to establish a research agenda to answer important public health questions about vitamin D, and as the basis of a conference planned for September 2007 with the goal of presenting a balanced overview of the available evidence on the efficacy and safety of vitamin D as an update to the 2003 NIH Conference on Vitamin D and Bone Health.

- For more information, see <http://vitamindandhealth.od.nih.gov/>
- For more information, see <http://ods.od.nih.gov/Research/EvidenceReports.aspx>
- (E) (ODS)

Multidisciplinary and Interdisciplinary Research

Microneedle-Based Immunization Against Pandemic Influenza: NIH is supporting a team of investigators under the Bioengineering Research Partnership grant mechanism to develop a low-cost, room temperature-stable, microneedle-based trans-dermal vaccine patch that could be rapidly distributed through pharmacies, fire stations, or the U.S. mail and self-administered in a painless manner by patients. This dose-sparing delivery system will not produce any sharp, biohazardous waste and would avoid the expensive and time-consuming hypodermic

vaccination process administered by medical personnel, thus allowing for a rapid pandemic influenza response. This innovative application impacts the U.S. Department of Health and Human Services Pandemic Influenza Response and Preparedness Plan and NIH's directives on High Priority Influenza Research Areas.

- For more information, see <http://www.hhs.gov/nvpo/pandemicplan>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIBIB)

Systems Biology and Systems Genetics: NIH launched the Integrative Cancer Biology Program to focus on networks that can be measured, modeled, and manipulated rather than individual components. Multidisciplinary teams are critical to integrating the disciplines of biology, medicine, engineering, mathematics, and computer science (e.g., computational biology). 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* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NCI)

Critical Issues in eHealth Research Conference: Toward Quality Patient Centered Care (September 2006): This second of two eHealth conferences served three purposes: (1) to highlight research methodologies that intersect across information technology, health communications, behavioral science, medical science, and patient care research, (2) to showcase existing and emerging technologies relevant to communications among patients and their health care teams, and (3) to discuss conceptual issues related to patient-centered eHealth research.

- [Atienza AA, et al Am J Prev Med 2007;32:S71-4](#), PMID: 17466821
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (OBSSR, NCI, ODP/ORD)

Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences: Merging scientific insights and technologies gleaned from behavioral and social sciences with approaches from other scientific disciplines offers the promise of further advancing the public health mission of NIH. This NIH Roadmap initiative funds projects that develop new/innovative measures, methods, and technologies that support the integration of human social and/or behavioral science with other disciplines across varying levels of analysis.

- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp>
- (E) (Roadmap—all ICs participate)

Nanomedicine Development Centers (NDC): The structures inside living cells operate at the nanoscale (about 1/10,000 the thickness of human hair). Recent advances in nanotechnology, which refers to the understanding and control of materials at the nanoscale, have yielded new tools to probe and manipulate objects at the nanoscale. These tools, as well as a variety of newly engineered nanostructures, are starting to be used in biomedical research. Nanomedicine, an offshoot of nanotechnology, is a rapidly emerging, multidisciplinary field that was identified as one of the nine initial NIH Roadmap initiatives. In late 2006, NIH completed the establishment of a national network of eight NDCs after an intensive 2-year planning and application process that involved extramural stakeholders from scientifically and medically diverse fields. The overarching goal of these centers is to understand and control the nanomachinery inside living cells in order to diagnose or treat disease and repair tissue. The work at these centers, which involve over 120 biomedical researchers located in 30 institutions, 12 States, and 6 countries, is geared toward understanding the fundamental properties of intracellular structures with great precision so that highly specific treatment or possibly even replacement of these structures can be achieved with

few or no side effects. Unlike traditional, translational research targeting a specific medical problem, these centers are beginning with basic science studies and, over a 10-year period, will apply their tools, technologies, and newly developed structures to a variety of disease or wound conditions that will be identified in parallel with, and as a consequence of, the technological developments. It is expected that this novel approach will stimulate the emergence of nanomedicine as a major contributor to improving human health in a variety of medical specialties.

- For more information, see <http://nihroadmap.nih.gov/nanomedicine/index.asp>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (Roadmap—all ICs participate)

NIH Roadmap Interdisciplinary Methodology and Technology Summit: The purpose of this NIH Roadmap Summit (August 2006) was to identify opportunities for developing research methodologies and technologies at the intersection of behavioral and social sciences with other disciplines. Topics discussed at the meeting included the following: large complex datasets, multilevel approaches, intergenerational approaches, economics/econometrics, Geographical Information Systems and neighborhood data, ecological momentary assessment, and combining qualitative and quantitative methods.

- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/summit0806/>
- (E) (Roadmap—all ICs participate)