The National Institute of Biomedical Imaging and Bioengineering Marks Its First Five Years[1]

Roderic I. Pettigrew, PhD, MD, Karen P. Peterson, PhD, William Heetderks, MD, Belinda Seto, PhD

This year, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) celebrated a very successful first 5 years as a congressionally appropriated member institute of the National Institutes of Health (NIH). The mission of the NIBIB, the newest member institute of the NIH, is to improve health by leading the development and accelerating the application of biomedical technologies. The NIBIB was created to provide a home for the discovery of new technologies, new techniques, and new approaches to solving the major challenges that we face in the health care system today. In particular, the Institute focuses on biomedical imaging, bioengineering, and the nexus of the quantitative sciences and the life sciences.

THE FIFTH ANNIVERSARY CELEBRATION

To highlight and celebrate the accomplishments of NIBIB-supported researchers and to inform the public about the present and future impact of technological innovation on health care in the 21st century, NIBIB held a day-long scientific symposium preceded by a kickoff dinner on May 31. Featured speakers at the dinner included former U.S. Surgeon General David Satcher and former U.S. Senator and Apollo astronaut Harrison Schmitt, the last man to have walked on the moon. The occasion also marked the first time that the NIBIB presented its Landmark Achievement Award, which was created to recognize watershed achievements in advancing health care through biomedical technology and to celebrate the scientists who made these contributions to the well-being of mankind. The 2007 award recognized the accomplishments of Paul Lauterbur, 2003 Nobel Laureate in Physiology or Medicine. Lauterbur received the Nobel Prize for his discoveries that enabled the development of magnetic resonance imaging (MRI). The posthumous award was presented to Lauterbur's widow, M. Joan Dawson, PhD, following Lauterbur's unexpected death in March 2007.

Advances in biomedical imaging and bioengineering highlighted the daylong symposium, held on June 1 in Bethesda, Maryland. The activities marked an important milestone in the Institute's history and provided a unique opportunity for stakeholders and fellow scientists to hear and learn from many great minds. The symposium's theme was "Changing the World's Health care through Biomedical Technology." It provided a platform for updating the public on the positive impact that technological innovation is having on health care, while recognizing the remarkable contributions of the physical science community to advancing medicine. In addition, it provided an opportunity for some of these scientists to share the personal stories behind these achievements. The symposium was opened with a stirring presentation by NIH Director Elias Zerhouni, who underscored the critical need for accurate and precisely defined biologic information across all spatial and temporal scales. Douglas Maynard, Stanley Baum, Shu Chien, and Robert Nerem recounted the historic struggle to create the Institute, as well as its achievements over the first 5 years.

Other distinguished speakers included Laser inventor and 1964 Nobel Laureate Charles H. Townes, MRI pioneer Waldo Hinshaw, and Institute of Medicine President Harvey Fineberg. Charles Townes captivated the audience as he recounted his discovery and development of the Laser and its antecedent, the Maser (microwave amplification through stimulated emission of radiation). Waldo

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[1] From the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, 31 Center Drive, 1C-14, Bethesda, Maryland 20892. Received October 15, 2007; accepted October 15, 2007. **Address correspondence to:** R.I.P. e-mail: pettigrr@mail.nih.gov

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Hinshaw delivered a Commemorative Lecture recognizing Lauterbur's work in MRI and noted that Lauterbur not only contributed to the science of magnetic resonance but also served as its champion. Harvey Fienberg cited the changing landscape of medicine, with the shift from acute to chronic diseases, the emergence of new diseases, and the great expectations for advances toward personalized health care through technological innovation.

Highlighting key technical advances, Anthony Atala, Director of the Institute for Regenerative Medicine, Wake Forest University; Ralph Weissleder, Director of the Center for Molecular Imaging Research, Harvard Medical School; and Dennis Spencer, Chief of Neurosurgery, Yale University, and his collaborator James Duncan, Chair of the Biomedical Engineering Program at Yale, shared progress in their respective fields. Atala described new methods to successfully engineer hollow organs such as the trachea, vagina, and bladder. Weissleder and his group have developed nanoplatforms able to image multiple biological processes at the cellular level using NMR. Spencer and Duncan's interdisciplinary team approach has improved epilepsy surgery outcomes and created new techniques to map the brain's electrical network, investigate brain structure, function, and biochemistry, and present this in an integrated and interactive three-dimensional display to help guide surgery in the operating room.

A common thread throughout the symposium was the importance of integrating ideas across disciplines, a concept commonly known as *interdisciplinary science*. Rensselaer Polytechnic Institute President Shirley Ann Jackson stressed the importance of introducing interdisciplinary training at the undergraduate level and acknowledged that NIBIB provides a critical linkage between engineering, computer science, and the biological sciences. An important event for the Institute, the symposium highlighted the history, mission, and direction of the Institute and illustrated the outcome of the Institute's work in leading the development of emerging technologies at the interface of the life and physical sciences.

ACCOMPLISHMENTS: THE FIRST 5 YEARS

The Early Strategy

To catalyze the building of its portfolio, NIBIB implemented an aggressive number of initiatives in 2003, covering a wide range of research topics that are representative of its major areas of focus. These included cellular and molecular imaging; advanced biomaterials; novel drug/gene delivery systems; tissue engineering; operation of sensors in vivo; improvements to imaging methods and technologies; telehealth technology development; image-guided interventions; low-cost imaging; small animal imaging; and scientist training as part of a joint program with the National Science Foundation (NSF). These initiatives generated a very robust response from applicants: over 1100 applications were received in response to these initiatives, half of which came from investigators who were new to NIH. The projects that were funded from these initiatives have formed a very productive research base for the Institute.

A key step in building the institute was the development of its Strategic Plan. Creation of the plan began in 2004, with the goals of setting a course for the Institute over the following 5 years with built-in flexibility to react as necessary to new developments on the biomedical research landscape. A unifying theme in the Strategic Plan is that of bridging the quantitative and life sciences. Major areas of research support under the Strategic Plan are nanotechnology applied to treatment of disease (nanomedicine); point-of-care technology development; image-guided minimally invasive interventions; regenerative medicine; optical imaging, biophotonics, and biosensors; large-scale bioinformatics and data acquisition technology development; low-cost diagnostic and therapeutic technologies; and telehealth. The components of the plan represent important areas of research that are critical to the mission and realizing the vision of the Institute.

NIBIB has also placed a great emphasis on outreach efforts to the extramural research community. This effort was established to aid the Institute's primary constituents, communities not traditionally well supported by the NIH, to become more familiar with and successful in obtaining NIH funding. Staff from Scientific Programs and the Office of Science Policy and Public Liaison have planned and participated in a series of regional grantsmanship seminars, at a rate of two per year, in different locations across the United States. The goal of these seminars is to provide potential applicants with useful information about the grants process at NIH, from grant preparation to submission and review. In addition, exhibits with information about the Institute and its research are shown at major scientific meetings throughout each year. To date, over 30 such exhibits have been shown.

Special Policies

The Nagy Award

The NIBIB has taken an aggressive approach to encourage applications from and support of new investigators—both those who are in the early stages of their careers and those who are new to the NIH. To help achieve a greater level of new investigator funding success, the NIBIB created a policy for new investigators that allows for funding of applications within an additional 5 percentile points of the current payline. This added margin increases the success rate of new applicants for the important R01 awards and applies both to program announcements calling for R01 applications and to unsolicited R01 applications. In honor of the late Edward C. Nagy, and his critical commitment to biomedical research, NIBIB has renamed its award for new investigators to the Edward C. Nagy New Investigator Award. Mr. Nagy, executive director of the Academy of Radiology Research until his death in 2006, was one of several people without whom the legislation that created NIBIB would not have been enacted.

These efforts to bring new investigators into the NIBIB have been very successful. Between 2002 and 2006, NIBIB has supported 165 new R01 investigators (applicants who have not received an R01 award before but may have received an R03, R15, or R21 award previously). In addition, NIBIB has funded 244 new R21 investigators—these awards were their first ever from NIH—during this same time period. These new investigators form a critical population of researchers in support of our mission.

High risk and team science

NIBIB has developed policies tailored to achieving its core goals of funding research at the interface of the quantitative and life sciences and supporting technological innovation. The research community has been concerned over the years that the peer review system favors more incremental, conservative research projects, and this approach is unsuited to many innovative projects at the interface of the life and physical sciences. In response to these concerns, NIBIB has established a goal of funding two or more R01 applications each year that focus on groundbreaking or highly innovative ideas and receive good scores but miss the established NIBIB payline due to issues over proposed experimental details and an associated increased level of risk. In addition, applications that similarly miss the established payline but are remarkable in demonstrating an interface or bridge between the quantitative sciences and the biological or behavioral sciences may also be funded under this policy.

Bridge awards

After several years of essentially flat NIH funding, there was a growing concern that some recently established research groups would, as a result of limited funding, have to dissolve or reduce collaborative team members. In response to this concern, a policy was established that provides 1 year of “bridge funding” at the level of the preceding year for new investigators who are applicants seeking their first R01 renewal. Investigators are eligible if they missed the established payline by 3% or less and the application has one more opportunity for review. Congressional funding in fiscal year 2007 (FY07) targeted specifically toward the study of “at-risk” research populations triggered the creation of a similar policy across the NIH. This policy applies to both established and new applicants whose application scores were near an institute’s payline and who had less than $200,000 in total annual funding from other sources.

CURRENT AREAS OF RESEARCH EMPHASIS AT NIBIB

NIBIB seeks to translate technological advances into solutions that improve human health by reducing disease burden and enhancing quality of life. Scientists from disparate disciplines are now being called upon to form interdisciplinary teams, with each team member making a uniquely critical contribution to the overall project. With over 800 active awards, NIBIB supports a broad range of research and training activities in areas including MRI, CT, optical imaging, ultrasound, molecular imaging, medical devices, biomaterials, tissue engineering, biomedical sensors, and bioinformatics. A sample of current activities is given next.

Quantum Grants Program

The Quantum Grants Program was launched in fiscal year 2006. This signature program supports interdisciplinary and large-scale research on projects that strive to develop solutions to major health care problems. The term “quantum” was chosen because it best exemplifies the difference that these select projects are expected to make—progress must be significant; a real “quantum leap” must be made. Projects in this program must seek to solve or significantly improve the management of a major medical problem that poses a high burden of illness on the population, or to resolve a highly prevalent technology-based major medical challenge. To date, NIBIB has funded five Quantum projects, covering a wide range of ground-breaking technologies, including regenerating damaged brain cells and blood vessels for the treatment of stroke, development of disposable microchips for the diagnosis of metastatic lung cancer, development of a bioartificial kidney to eliminate conventional dialysis, development of multifunctional nanoparticles to assist in removal of brain tumors, and development of insulin-producing cells to treat diabetes.

Point-of-Care

Empowering clinicians to make decisions at the initial point of physician contact, or the point-of-care (POC), has the potential to profoundly impact health care delivery and also help address the challenges of health disparities. The success of a potential shift from curative to predictive, personalized, and preemptive medicine could rely on the development of portable diagnostic and monitoring devices for near-patient testing. The NIBIB has contributed to advances in this area by funding the development of sensor and platform-based microsystem technologies. These instruments combine multiple analytical functions into self-contained, portable devices that can be used by nonspecialists to rapidly detect and diagnose disease and can enable the selection of a definitive therapy during the visit to the physician.

Molecular Imaging

Achieving the goal of a medical paradigm shift from a focus on curing disease to a focus on preempting disease or its serious consequences requires the ability to detect and monitor pathologic processes at the molecular level. Indeed, designing, monitoring, and tailoring optimally effective treatments also will require molecular imaging. Consequently, the NIBIB actively supports research in this area, focusing on probe development based on a spectrum of modalities, including nuclear, MRI, ultrasound, CT, and optical. Also, molecular imaging was identified as a priority area in the NIH Roadmap for Medical Research. Two initiatives, “Innovations in Molecular Imaging Probes” and “Development of High Resolution Probes for Cellular Imaging,” were developed and released. The goal of these initiatives is to increase the sensitivity of the probe signal by 10- to 100-fold so as to enable observation of single molecular events in vivo.

Image-Guided Interventions

Advances in imaging and image processing have been largely responsible for the development and proliferation of minimally invasive surgical procedures as well as medical robotics. *Image-guided interventions* (IGIs) can be defined as procedures that integrate imaging technologies with clinical treatment at the point of patient care. IGIs minimize trauma and improve patient outcomes. They include 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 the area of IGI has been identified at multiple workshops sponsored by the NIH and other federal agencies. Workshop participants consistently identified as a major barrier the synergistic fusion of multimodality and multidimensional image datasets into a highly unified form that describes more accurately and extensively the complex nature of human anatomy, physiology, biology, and pathology. Other research challenges included the development of low-cost technologies and the development of standards and validation methods for IGI technologies. In response, in August 2006, NIBIB and NCI issued in a joint request for applications to support the first phase of a two-phase project that will deliver high-impact IGIs. Multiple responsive applications have now been funded.

Optical Imaging

Optical imaging is an emerging new biomedical technology with great potential for improving disease diagnosis and treatment. Rapid advances and developments in biophotonics—the science and technology of the interaction of photons within and on biological systems—during the past 15 years have resulted in promising innovations with broad applications in high-resolution imaging. More recent advances in genetics and genomics have spurred applications to image cellular activity, such as visualization of gene expression in real-time, as well as detection of protein synthesis during biologic processes. The ability to image, analyze, and manipulate living tissue at the cellular and molecular levels can enhance the practice of medicine, making it more predictive, personalized, and preemptive. However, optical imaging techniques are still primarily laboratory based. The transfer of these new techniques into clinical tools remains a challenging problem and requires close collaboration between imagers, engineers, clinicians, mathematicians, and basic scientists. The translational research of in vivo optical imaging is an important research focus for the Institute.

Regenerative Medicine

Regenerative medicine and tissue engineering represent a critical and highly visible frontier in biomedical and clinical research and are marked by recent unprecedented scientific advances. The creation of living, functional tissues to repair or replace lost tissue or organ function due to age, disease, damage, or congenital defects opens the door to the treatment of debilitating diseases and disorders for which current treatments are limited or nonexistent.

The ultimate goal in an ongoing multiagency initiative in which NIBIB plays a lead role is to engineer functional tissue in the laboratory (in vitro) for implantation into humans (in vivo) or to foster tissue regeneration directly in vivo. Because tissue engineering is an emerging multidisciplinary field at the interface between the life and physical sciences, NIBIB plans to provide continued resources to foster the science needed for this field to mature and for translation of important breakthroughs from basic research to clinical studies and ultimately to patients.

Nanotechnology

The term *nanotechnology* is used to describe many types of research at the atomic, molecular, or macromolecular level. Research in this area can provide a fundamental understanding of phenomena and materials that enable the creation and use of structures, devices, and systems that have novel properties and functions because of their extremely small size. Today, biomedical researchers are working at the microscale and nanoscale levels to diagnose disease and to develop new drug delivery methods, therapeutics, and pharmaceuticals.

The NIBIB is continuing its efforts to support research that encourages technology development projects with the potential to facilitate and accentuate the translation of discoveries in nanoscience and nanotechnology to biomedical products for diagnosis and therapy. For example, the NIBIB supports research aimed at the design and fabrication of electronic, optical, and fluidic components for microelectromechanical systems (MEMS) that enable fundamental studies of multiple biosensing platforms. The goal is to design integrated systems that provide "sample-to-answer" capabilities—from sample preparation to detection to data processing and output—relevant to a given clinical problem, like blood glucose sensors for diabetes.

Training Investigators

An important goal of the NIBIB is to train a new generation of researchers equipped to meet the modern needs of interdisciplinary and transdisciplinary research. The Institute's proactive approach is to develop creative and flexible opportunities that will fill critical gaps in the career continuum while also enhancing the participation of underrepresented populations. Attracting students at various points in their education to research careers in bioimaging and bioengineering, and providing training opportunities to these researchers, are major goals. Several different approaches have been taken to achieve these goals.

Early career investigators are the innovators of the future, because they bring fresh ideas to existing biomedical research programs and pioneer new areas of investigation. Their successful transition to independence and their success in obtaining NIBIB funding is therefore a major priority of the Institute. In the spirit of fostering new investigator development, NIBIB has partnered with the Howard Hughes Medical Institute (HHMI) to support the HHMI-NIBIB Interfaces Initiative. This is a university-level program that provides PhD scientists with the knowledge and skills needed to effectively conduct research across scientific disciplines. Institutions participating in this initiative will be expected to develop "best practices" models for use by other institutions. The new cadre of scientists trained in this program will be at the forefront of progress in biomedical research that increasingly relies on the input of new ideas, methodologies, and investigative strategies from the physical sciences, engineering, and mathematics. The program is expected to reduce existing barriers to interdisciplinary graduate science education.

NIBIB continues to look for innovative ways of attracting outstanding clinicians to research careers at the interface of the life and physical sciences. Since 2004, NIBIB has issued a Program Announcement annually for research supplements to promote clinical resident research experiences. This initiative was the result of recommendations made at NIBIB workshops on bioengineering and biomedical imaging training. Candidates for the supplements must have health professional degrees and must be

Table 1
Growth of Awards Made and Numbers of Grantees Funded from 2002 to 2006

	NIBIB Grantees in First 5 Years		
	FY2002	FY2006	% Increase
Awards	285	809	184%
Grantees	215	714	232%
Budget	$111,861	$296,810	165%

enrolled in a clinical residency program in the United States. These research supplements, made to existing research grants funded by NIBIB, provide 1 to 2 years of critical research experience for medical residents.

NIBIB also works with other federal agencies to develop training programs. The NIBIB/NSF Bioengineering and Bioinformatics Summer Institutes are designed to attract undergraduate and graduate students to bioengineering and bioinformatics careers. The Biomedical Engineering Summer Internship Program provides undergraduate bioengineering students the opportunity to participate in cutting-edge research at Intramural NIH laboratories. The NIH/NIST Joint Postdoctoral Program provides serial postgraduate research experiences in the biological and physical sciences at both agencies.

GROWTH IN THE NIBIB PORTFOLIO

The programs and policies described here have resulted in the development and maintenance of a diverse portfolio of funded projects at NIBIB (Table 1). Despite the overall flattening of the NIH budget during the years 2002 to 2006, NIBIB made notable strides in the number of awards made and the number of grantees funded. From 2002 to 2006, the NIBIB budget grew from $111.8 million to $296.8 million, an increase of 165%. However, greater increases were made in numbers of awards made during this period (from 285 to 809, or 184%) and numbers of grantees funded (from 215 to 714, or 232%).

The Intramural Program at NIBIB

The Intramural Research Program at NIBIB is undergoing dramatic growth and transformation. Dr. Richard Leapman, former acting director of the Division of Bioengineering and Physical Science (DBEPS) in the NIH Office of Research Services, was hired by NIBIB in 2006 to be the Scientific Director of the Intramural Research Program. Dr. Leapman's research interests include the development and application of quantitative electron microscopy and the application of novel nanoscale imaging methods to structural and cellular biology. Very recently, the entire Division of Bioengineering and Physical Science was transferred to the NIBIB Intramural Research Program. This division specializes in the development and application of new technologies, based on engineering, mathematics, and the physical sciences, for the solution of problems in biology and medicine. Consultations and collaborative research with other NIH intramural scientists will be the main focus of this group's work. Program areas include supramolecular structure and function, dynamics of protein assembly, complex biological systems, immunochemical nanoscale analysis and diagnostics, pharmacokinetics and drug delivery, and noninvasive optical imaging. The new intramural component joins the existing NIBIB Intramural Research Program, which includes the PET Radiochemistry Research Laboratory responsible for conducting research and training in the development and application of novel radiochemical probes for biomedical imaging, and the joint Laboratory for the Assessment of Medical Imaging Systems at the FDA. This addition marks an important milestone in the history of the NIBIB.

LOOKING FORWARD

The NIBIB, in partnership with industry, academia, and other federal agencies, will continue to lead the development of revolutionary technologies that will improve public health and reduce suffering due to injury and illness. We envision advancing technologies that will detect early, preclinical, molecular events that identify patients at risk for developing disease; the development of smart sensors that utilize physiologic signals from the body to release drugs at appropriate sites, in appropriate doses; engineering living tissue that is capable of growth and normal function that can be used to repair or regenerate damaged tissues or organs; personalized, minimally invasive or noninvasive medical therapy for individuals; and new approaches to facilitate the quantitative understanding of the relationship among elements of complex biological systems and integration across biological scales, from the gene to organ to the entire body.

NIH Director Elias Zerhouni observed at the NIBIB Anniversary Symposium that "Innovation and creativity are inherent human qualities." The history of science and the ability to make measurements have occurred in parallel over time. Better quantitative tools can allow more scientific insight to be gained; conversely, more scientific insight drives the need for better quantitative tools. As our understanding of disease processes grows, we are finding that diseases that were thought to be very different and separate from each other actually have common pathways. This change in our conceptualization of disease requires new approaches to prediction, detection, treatment, and prevention. Biomarkers, quantitative tools, sensors, and other technological innovations are all necessary components of new strategies that will be developed in response to this new approach to understanding disease. Technological innovation, therefore, is the engine of scientific progress, as well as a means of bridging the gap between what is possible and what is delivered to the public. At NIBIB, we are proud to be a part of this exciting venture.