Biomedical Imaging Symposium:
Visualizing the Future of Biology and Medicine

Natcher Conference Center
National Institutes of Health
Bethesda, MD
June 25-26, 1999

Sponsored by
NIH Bioengineering Consortium (BECON)
American Institute for Medical and Biological Engineering (AIMBE)
Radiological Society of North America (RSNA)

Executive Summary

Advances in the imaging sciences could change the face of medicine, making it possible to non-invasively detect, diagnose, and guide therapy for a large variety of diseases. Research on biomedical imaging is already a large part of the NIH agenda, and we invited a group of experts to advise NIH on the most exciting directions for future investment in imaging research. Some of the goals of the Symposium were to:

- Identify the most important challenges and opportunities in biomedical imaging science; and
- Develop strategies for integrating imaging science with biological and medical research.

Symposium speakers and audience participants developed the following recommendations to achieve these goals.

1. Multidisciplinary Research Programs
An important challenge is to encourage and facilitate the establishment of multidisciplinary research and development programs in biomedical imaging, with specific emphasis on molecular imaging or image-guided therapy.

2. Imaging Technology, Probes, and Contrast Agents
Recent discoveries present a significant opportunity to foster the development of new biomedical imaging technologies and the molecular probes and contrast agents that are the tools for linking imaging to specific biological processes.

3. Education and Training
New training programs in molecular imaging are needed to create a generation of scientists for whom the principles of imaging, physics, bioengineering, molecular

biology, physiology, pharmacology, and pathophysiology form an intellectual continuum.

4. Clinical Trials and Informatics
Clinical studies, with careful attention to integration of informatics, are needed to assess biomedical imaging technologies and to advance biomedical imaging research.

5. Relationship between NIH, FDA, HCFA, and Industry
Greater cooperation among NIH, FDA, HCFA, and industry (both large and small businesses) would improve the speed with which new imaging technologies, probes, and contrast agents can be transferred into clinical practice.

Biomedical Imaging Symposium Report

This second annual BECON symposium was designed to enlarge on the ideas first discussed in the 1998 meeting, *Bioengineering: Building the Future of Biology and Medicine*. Attendees from academia, government, and private industry participated in plenary sessions, panel discussions, and scientific poster sessions and exhibits focussed on state-of-the-art technology and applications in the field of Biomedical Imaging.

Objectives:
- Identify the most important challenges and opportunities in biomedical imaging science;
- Develop strategies for integrating imaging science with biological and medical research;
- Provide a forum for interdisciplinary imaging scientists to discuss the vision and future of biomedical imaging;
- Recommend areas of future investment to NIH.

Three general topics were addressed. These were imaging at the cellular and molecular levels; imaging in the early detection, staging, and recurrence of disease; and imaging in therapy for various diseases. Speakers and audience members provided the NIH with recommendations regarding the use of imaging sciences in medicine, mechanisms to enhance research and development of imaging technology, and the imperative for preparing a future generation of imaging scientists.

Imaging at the Cellular and Molecular Level

Symposium speakers described recent advances in imaging at the cellular and molecular level in two broad categories. Optical coherence tomography, ultrasound and magnetic resonance imaging (MRI) were discussed as examples of cellular imaging technologies where increased spatial resolution has given us new windows into the anatomy, cell

structure, and histopathology of living tissues. These imaging modalities are noninvasive or minimally invasive and can be used to take serial "virtual biopsies" or snapshots of target organs and tissues in living animals over time. Positron emission tomography (PET), MRI, fluorescence spectroscopy, or nuclear medicine techniques are examples of the detection methodologies used with molecular probes and contrast agents, and typify the powerful new field of molecular imaging. Molecular probes are often signal-producing agents linked to drugs or proteins, and are designed to be specific for a particular molecule or biological process. A probe may also be introduced as a gene that codes for an optically active protein or contrast agent-binding receptor when expressed. An example would be [^{18}F]fluoroethylspiperone, a molecular imaging probe that binds to the dopamine D2 receptor. A PET image would show only those tissues where the D2 receptor is found on the cell surface. Another example is a caged gadolinium molecule, which changes conformation and becomes an MRI contrast agent in the presence of calcium.

It is very exciting that along with the deeper understanding of disease afforded us by molecular biology and genetic research comes the potential to visualize these processes with molecular imaging. Molecular information has profoundly affected our approach to diagnosing and treating disease, and many diseases are being redefined in terms of the their characteristic genetic or molecular abnormalities. Likewise, new therapies are designed to specifically target the abnormal gene or phenotypic pathway. There is a concomitant need for non-invasive or minimally invasive imaging procedures that will provide the information to make these molecular diagnoses or track the effects of these targeted therapies at the molecular level in patients. Molecular imaging techniques are already used in isolated cells, tissues, and animal models, and are being developed for use in humans.

The science of molecular imaging needs further development as a research tool in small animals and humans, and it needs to be refined for routine clinical use. This will require close collaboration between basic scientists who make the molecular discoveries and the imaging scientists who can create useful imaging procedures. In addition to significant improvements in the spatial, contrast and temporal resolution of imaging device sensors, chemists will need to create the diagnostic imaging probes that will amplify the molecular signals and add chemical specificity to the detected events. Team science is essential for these advances to occur. A challenge for NIH is to facilitate and support the multi-disciplinary efforts needed to bridge these gaps.

Imaging in the Early Detection of Disease

Outcome of therapy often depends on early detection in a symptomatic patient, fast diagnosis, and accurate, careful staging of his disease. Imaging technology, such as MRI, ultrasound, x-ray and Computed Tomography (CT) scanning have become standard tests in disease detection and patient management. New clinical modalities with improved sensitivity are on the horizon, including PET and MRI functional brain imaging for neurological disease, MRI cardiac function imaging, contrast-enhanced MRI for breast and other cancers, and high resolution three-dimensional ultrasound for breast cancer,

prenatal examination and heart function. While imaging capabilities are becoming more sensitive, thus detecting a greater percentage of lesions than ever before, they need to provide more specific biological characterization to improve our fundamental understanding of disease and provide a diagnosis more specific to the development, selection, and evaluation of therapies.

Public health is improved by population-based screening for disease, but these screens must be fast, inexpensive, easy to administer to very large numbers of people, and rely on technology that can be widely distributed. They must also be highly specific and turn up few false positives and even fewer false negatives. Low specificity of diagnostics is a major problem in current early-detection methods, both for symptomatic patients and for population-based screening. For example, new technology that overcomes the low specificity of current screening methods for cervical, breast, prostate, colon, lung, and skin cancer would significantly lower the cost of diagnosis and therapy. Likewise, the incidence of death and impairment could be reduced if stroke and coronary patients could be evaluated in the emergency room quickly and accurately for their likely response to existing therapies.

In order to enhance our ability to detect disease at its earliest stages, scientists must determine how to define disease better in terms of the specific molecular and genetic abnormalities underlying the symptoms. Novel imaging technologies are needed to pinpoint signifying events that mark disease onset and define its biologic characteristics. Scientists also must determine the most effective types of imaging modalities for different diseases, including diseases with very low incidence and prevalence which are often difficult to detect. Improved quantification of imaging test results is also important for standardization and comparison purposes, allowing us to better monitor therapy or disease progression.

NIH institutes could identify the diseases of interest where patients would benefit from increased specificity of early detection. These diseases would represent areas of particular opportunity for imaging technology development, implementation and dissemination. NIH Institutes could initiate discussions with manufacturers, researchers, and clinicians to develop these priorities, and to alert and educate the research community about these high priority areas.

Imaging in Therapy

Several decades of advances in the imaging sciences have demonstrated that imaging has become an important, if not critical factor, in the care of patients. We are now witnessing a far-reaching change in image-guided therapy. This "revolution" is based on synergistic interactions among scientists from many disciplines. In the symposium, image-guided therapy was explored from the point of view of the surgeon, the radiologist, the researcher, the bioinformatics specialist, and the bioengineer. Imaging in therapy encompasses an enormous variety of technologies. These include use of multiple imaging modalities for diagnosis and position of the lesion in three-dimensional space, real-time imaging of anatomy, physiology (e.g., blood flow, neuron activation) and

function during surgery, video imaging in laparoscopic surgery, image-guided placement of catheters and other devices, and surgical computer-aided design and distance medicine. There are new interventional imaging techniques such as thermal coagulation via focused ultrasound. Molecular and other imaging modalities can be used to monitor drug delivery and action, gene expression, or metabolism. Serial imaging studies are used to monitor response to therapy for tumors. Developments in hardware and software in CT, MRI, ultrasound, PET, and single photon emission computed tomography (SPECT) in concert with clinician-directed applications have made this possible.

The various sciences underlying this field must be rigorously investigated to maximize the benefits that improved imaging modalities can bring to delivery of health care. Within academic health centers, however, image-guided and computer-assisted intervention does not have a clearly defined structure or home. This makes it difficult to establish a targeted grant applicant pool or criteria for research and clinical training. Therefore, the challenge is to develop a multidisciplinary approach, similar to existing Centers of Excellence, that will break down traditional barriers, foster collaborative interactions, and harness these technologies for hypothesis-driven research.

RECOMMENDATIONS

Discoveries in molecular biology and advances in imaging technology present an extraordinary opportunity for biomedical imaging to play an increasingly important role in all aspects of medicine. The challenge for NIH is to ensure the timely translation of new imaging methodology into clinical practice in a way that improves the quality and affordability of healthcare. Important investments for NIH would be increased support for truly innovative imaging research, and encouragement for researchers to address those issues--reproducibility, efficient patient throughput, data analysis and interpretation--which allow for widespread implementation of new technology.

In order to achieve these goals, it must be recognized that imaging science encompasses a variety of disciplines including medicine, biology, physics, chemistry, engineering, and bioinformatics. Continued success depends on highly trained, multidisciplinary teams as well as adequate resources for development and testing. Biomedical imaging therefore provides an ideal opportunity for productive collaboration between government, private industry, healthcare providers and academia.

1. Multidisciplinary Research Programs

An important challenge is to encourage and facilitate the establishment of multidisciplinary research and development programs in biomedical imaging, with specific emphasis on molecular imaging or image-guided therapy.

Multidisciplinary programs are essential in order that discoveries being made at the molecular and sub-molecular level be translated into new imaging methods for disease

detection, diagnosis, and therapy. Recent Program Announcements such as "Bioengineering Research Partnerships" (http://grants.nih.gov/grants/guide/pa-files/PAS-99-010.html) and "Bioengineering Research Grants" (http://grants.nih.gov/grants/guide/pa-files/PAR-99-009.html) indicate that NIH recognizes the value of multidisciplinary research that includes a strong bioengineering component. Current funding mechanisms include collaborative Interactive Research Project Grants that use the R01 mechanism (http://grants.nih.gov/grants/guide/pa-files/PA-96-001.html), and R24 grants (Resource-Related Research Projects). Additional programs are needed to encourage collaboratory projects between biologists, chemists, physicists, pharmacologists, computer scientists, bioengineers, and clinicians.

A challenge for NIH initial review groups (IRGs) is to facilitate multidisciplinary participation in cellular and molecular imaging research. Relevant review panels should include experts in the various physical and biological scientific disciplines that comprise the field of biomedical imaging. Another challenge for NIH is to become receptive to applications where a single project is led by multiple equal principal investigators with complementary expertise.

The National Cancer Institute recently released an RFA for '*In Vivo* Cellular and Molecular Imaging Centers' (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-99-004.html). Similar programs focused on molecular imaging are needed for diseases other than cancer. Centers of excellence focused on image-guided diagnosis and therapy are also needed. These centers should be multidisciplinary and have multi-departmental support, and should combine onsite technology development with strong basic science and system engineering. Partnerships with industry are also desirable. The centers for image-guided diagnosis and therapy should develop a multi-faceted scientific program that might include research in basic development of medical imaging technology, computer science, targeted delivery systems for therapeutics, endoscopic and endovascular tools, microsensors, or molecular imaging probes.

2. Imaging Technology, Probes, and Contrast Agents

Recent discoveries present a significant opportunity to foster the development of new biomedical imaging technologies and the molecular probes and contrast agents that are the tools for linking imaging to specific biological processes.

Many of the important advances in biomedical imaging over the last decades (e.g., CT, ultrasonography, MRI, PET) originated from investigators with roots in disciplines such as physics, chemistry, engineering, and other areas that have not been well-represented in the mainstream of medical research. Among investigators who apply basic science to develop new imaging technology, there is a perception that this field of research is not well understood by funding bodies at the NIH and that the level of support is not commensurate with the level of impact that new imaging technology has had on research and medical care. A challenge for NIH is to fund early technical development of basic

and generic imaging technologies, before specific disease or organ-oriented applications are proven. Programs that will attract the necessary experts in chemistry, physics, molecular biology, pharmacology, and bioengineering to collaborate in these efforts are needed.

A related opportunity for NIH is to develop programs and review mechanisms that will enable engineers, physicists and chemists in the imaging sciences to participate more successfully in the open, peer-reviewed NIH system. This would allow them to fund their careers by the R01 mechanism, just as the biological scientists have been able to do for many years. A challenge will be to dispel the notion that research directed at development of technology is intrinsically less meritorious than studies of biology or pathophysiology.

Molecular probes and contrast agents are the tools that link an imaging device to specific biological processes of disease. These agents serve to selectively 'light up' a specific region, tissue, lesion, or cell because of some novel aspect of its particular biology. Future success in molecular imaging will proceed directly from a timely investment in the design of these reagents. Funding will be required not only for research and development, but also to train people capable of designing and developing novel imaging probes. Molecular probes should be specific for biological processes such as gene expression at the level of transcription or translation, signal transduction (cell surface receptors), enzyme action or other metabolic processes, blood flow, or drug action. Of particular importance are molecular imaging probes that are minimally invasive and allow tissues in animals and people to be monitored in vivo, and in real time. These will be used for disease detection, diagnosis, and ultimately, for guiding treatment. They will serve as tools in basic research and drug development, as well as in the design of trials in preclinical models of disease and in patients.

Supporting molecular imaging probe design and synthesis using such approaches as combinatorial and parallel chemistry and high throughput chemical screening technologies is an area of important opportunity. Likewise, the development of in vivo molecular imaging technologies for screening molecular imaging probes and drugs in genetically engineered mouse models of human disease are worthy areas for investment.

Cooperative efforts between universities, other not-for-profit organizations, such as DOE and NSF, and the pharmaceutical industry in developing molecular imaging probes should be encouraged. These partnerships should be especially useful in drug studies and other forms of clinical research. Imaging of drug biodistribution will facilitate drug discovery, validation and efficacy, and the approval process. Molecular probes may help elucidate any changes in the biological systems targeted by drugs. Molecular imaging probes will hopefully be used as surrogate markers to help assess the outcome in clinical trials of new therapies that span the spectrum from gene therapy to conventional drugs.

Support for the preparatory work required to obtain Investigational New Drug (IND) approval for probes and contrast agents is needed. Molecular imaging agents are likely to be highly specific for a particular application, and may therefore not have large market

potential. Industry may have limited motivation to support the necessary work involved in IND preparation. If this support is not provided, most of these potential agents will never reach clinical trials.

3. Education and Training

New training programs in molecular imaging are needed to create a generation of scientists for whom the principles of imaging, physics, bioengineering, molecular biology, physiology, pharmacology, and pathophysiology form an intellectual continuum.

Traditional scientific training programs are designed to teach traditional disciplines. New training and educational paradigms are needed to prepare scientists for the type of interdisciplinary research required for success in the imaging sciences. These scientists will need chemistry, physics, molecular biology, pharmacology, and bioengineering so that they can understand the principles of medical imaging, probe targeting and development, tracer methodologies, normal physiology and the process of disease. The need for scientists with this type of integrated education is expected to grow along with the demand that molecular and cellular imaging take its place in the research toolbox of cutting-edge biologists.

New initiatives in training at the interface of molecular imaging, chemistry, physics, pharmacology, integrative physiology, and bioengineering must necessarily attract training faculty with a commitment to this integration. Needed are interdisciplinary graduate programs that provide the student with a continuum from the basic imaging physics, through the chemistry of molecular probes, to cellular and molecular principles, and extending into disease processes. The course content, laboratory experience, and research milieu of such programs must cross traditional disciplinary boundaries. Such training should be made available to students from the pre-doctoral to post-doctoral levels. These programs should also have the resources to provide postdoctoral training for qualified young researchers who have degrees in the traditional biological sciences, chemistry, or imaging/engineering disciplines. Finally, the fastest way to stimulate new research in this field is to provide for the continuing education of senior faculty who already command research resources, in order to bring to their current programs these new technologies and concepts at the interface of imaging and biology. Fellowships and sabbatical support for immersion experiences and for intensive didactic exposure should be made available to senior faculty.

Proposals for new interdisciplinary bioimaging training programs should be reviewed for merit by senior scientists from the various disciplines, to ensure that curricula encompass all the relevant scientific disciplines within the field of biomedical imaging. It is important that these reviewers understand and work within the multidisciplinary philosophy.

4. Clinical Trials and Informatics

Clinical studies, with careful attention to integration of informatics, are needed to assess biomedical imaging technologies and to advance biomedical imaging research.

Clinical trials of new imaging technologies and new imaging probes are essential and require considerable resources. There is a challenge for government and private entities to collaborate on funding and conducting the necessary clinical trials of biomedical advances. Many clinical trials are performed for reasons other than testing imaging modalities, but use imaging as part of the trial. These present an opportunity and a challenge to ensure that the biomedical imaging used in the trial is state-of-the-art technology. Furthermore there is a challenge to NIH to provide leadership in establishing standards for recording image data, and to employ these standards in all its clinical research.

Informatics, an essential component of biomedical imaging, concerns the collection and processing of imaging data for use in research and medicine. It also refers to the establishment and management of large databases of imaging information, and to the process of extracting information from them. Rapid evolution of medical procedures in general and medical imaging in particular has led to a gap between the mass of clinical information a clinician must synthesize, and the technology available for integrating this deluge of information into a coherent, readily interpretable picture. Today, an unparalleled opportunity to fill this gap arises from cheap powerful computers and networks, the transfer of image analysis methods from military and space agencies to civilian use, and the increasing availability of digitally stored clinical imaging data.

Most extant imaging databases have been developed by individual research organizations. Data are stored in incompatible formats, and images from one cannot be compared with those from another. No widely accepted formats or standards have evolved for collection and storage of three-dimensional data. Therefore, a system to standardize imaging information is greatly needed, along with national databases to archive, organize, and retrieve data. These resources will be invaluable for the validation of new diagnostic technologies so that they can become clinically useful.

The following areas of opportunity were identified by speakers at the Symposium:

- interdisciplinary collaborations are needed to develop new informatics-based systems and models that integrate clinical and biomedical imaging data to support medical decision-making;
- databases are needed that contain both biomedical images and pathology or other outcome and clinical data. These should comprise an adequate number and distribution of cases to address institute priorities. Databases would be used, for example, in testing and validation of disease-specific, computer-aided image analysis methodologies. This effort should include standards for acquiring data, specifications

for data compression and storage, standards for nomenclature, and standards for database structure so that investigators can work across multiple databases;
- computer-aided image analysis methodologies are needed for increasing the specificity of current clinical imaging methods;
- biostatistics components are needed in all image analysis programs to better quantify the results of imaging tests;
- informatics and computer science could be integrated into funding priorities, program announcements, and other aspects of research, education, and training.

There is an opportunity for NIH to collaborate with other agencies or exert leadership in any or all of the above areas. NIH could hire staff or use external advisors with expertise in systems design, process engineering, and informatics at all levels of the organization, from review groups through institute policy and planning. Potential research methods could be evaluated against such design criteria in order to make good choices to use in expensive animal and clinical testing phases. NIH could also make such expertise available to clinical trial groups planning to test biomedical imaging or engineering objectives and foster interdisciplinary collaborations that bring systems expertise from engineering and informatics together with the appropriate expertise in biomedical imaging, medicine, biology, chemistry, pharmacology, and/or technology development.

5. Relationship between NIH, FDA, HCFA, and Industry

Greater cooperation among NIH, FDA, HCFA, and industry (both large and small businesses) would improve the speed with which new imaging technologies, probes, and contrast agents can be transferred into clinical practice.

We are currently seeing the rapid development of new molecular probes and contrast agents that allow biological processes to be imaged. Many such probes are now ready to be tested in phase I and II clinical trials. These compounds differ from pharmaceuticals in that they are designed to have no effect on the biological process under investigation. Also, many pharmaceuticals are given over sustained periods of time, whereas molecular probes are administered a few times at most. It would be an impediment to clinical research if these new molecules were required to go through the same regulatory requirements used to assess pharmaceuticals. The same standards of safety, but not the same process, should be applied to both probe molecules and pharmaceuticals (with adequate consideration of the extremely small amount of the molecular probe that is usually administered). On the other hand, different criteria must be used to assess the efficacy of probes versus drugs. Most importantly, these probes must be proven to accurately assess the biological process under study or the location, amount, and state of its specific recognition site.

Symposium speakers encouraged NIH to continue its communication with FDA and HCFA aimed at streamlining existing procedures that affect transfer of molecular imaging probes and other imaging technologies into clinical practice. These agencies could facilitate this process by developing efficient and effective ways for technology to

be evaluated, approved or discarded. Policies for physician and hospital reimbursement must be in place before approved technology can move fully into the clinical setting. Clinical implementation is a particularly difficult process for technologies that employ both an instrument and a biological imaging probe because both have to be reviewed and evaluated. Communication among NIH, FDA, HCFA, and industry, such as that recently promoted by NCI, could lead to streamlined technology assessment and minimize redundancy in the approval processes at FDA and HCFA.

Conclusions for Biomedical Imaging Research

The recommendations described above provide a blueprint to NIH to prepare for the challenges that accompany advancing research in biomedical imaging. There is a need for immediate and intelligent action in addressing the existing deficiencies in biomedical imaging research. The emerging new imaging technologies could very likely change the face of medicine, making it increasingly possible to noninvasively detect, diagnose, and guide therapy for a large variety of diseases. In order to make this potential a reality, NIH must encourage scientists with complementary expertise to join forces and invent new imaging technologies and new molecular probes of biological processes. The Universities are faced with the challenge of providing new multidisciplinary training programs in order to equip the next generation of scientists with the knowledge and skills necessary to develop such technology. Resources must be provided to build the bioinformatics tools necessary to fully exploit and allow widespread use of new clinically important imaging modalities. The NIH review community must recognize the merit of interdisciplinary, multi-investigator projects aimed at development of basic imaging technology. NIH should draw on its existing resources, as well as form partnerships with other agencies and industry to make biomedical imaging a more inclusive and productive field of inquiry. These efforts will establish the necessary bedrock upon which the future of biomedical imaging research can be built.