

# Special Report: Biomedical Imaging Research Opportunities Workshop IV—A Summary of Findings and Recommendations<sup>1</sup>

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**Editor's note:** *This editorial is being published in the February 2007 issues of Annals of Biomedical Engineering and Radiology so as to reach the readership of both journals. The full report, of which this Editorial represents a summary, appears in the February 2007 issue of Medical Physics.*

Anthony V. Proto, MD, Editor

The fourth Biomedical Imaging Research Opportunities Workshop (BIROW IV) was held on February 24 and 25, 2006, in North Bethesda, Maryland. BIROW IV was sponsored by the Academy of Radiology Research, the American Association of Physicists in Medicine, the American Institute for Medical and Biological Engineering, the Biomedical Engineering Society, and the Radiological Society of North America; it was cosponsored by 19 other medical imaging societies. The purpose of BIROW IV (BIROWs I–III were held in 2003 [1], 2004 [2], and 2005 [3]) was to identify and characterize opportunities for scientific research and engineering development in biomedical imaging. This article presents a summary of the findings and recommendations of BIROW IV; a full report is available in *Medical Physics* (4). Authors of the report-back sessions from which this summary has been prepared are Filip Banovac, MD, Paul L. Carson, PhD, Ralph A. DeFronzo, MD, William C. Eckelman, PhD, Gary D. Fullerton, PhD, Steven M. Larson, MD, Gordon McLennan, MD, and Michael J. Welch, PhD.

BIROW IV focused on four imaging areas that offer a spectrum of opportunities for scientific research and engineering development: Imaging of Rodent Models, Imaging in Drug Development, Imaging of Chronic Metabolic Disease: Diabetes, and Image-Guided Intervention in the 4th Dimension—Time.

Each topic was addressed in a plenary session in which four leaders in the field summarized the state-of-the-art science and presented their perspective on research opportunities. The plenary sessions were followed by audience breakout sessions in which participants explored relevant research opportunities and challenges. The findings and recommendations of the plenary and breakout sessions were compiled into reports that were discussed by the entire assembly on the second day of the workshop and subsequently synthesized into the paper published in *Medical Physics* (4). These findings and recommendations are also outlined in this summary report.

## Imaging of Rodent Models

Rodents serve as models of human disease and as test vehicles for guiding and evaluating novel diagnostic and therapeutic tools to improve the identification and intervention of disease. Imaging of rodent models provides insight into the molecular mechanisms of health and disease and enables researchers to monitor the evolution of disease over time and in response to various interventions.

## Research Opportunities

Imaging of rodents facilitates the qualitative and quantitative delineation of normal and disease-related biologic processes and permits these processes to be monitored over time and as they respond to physical and pharmacologic intervention. Research designs based on imaging offer distinct methodologic advantages and cost savings compared with techniques that require periodic sacrifice and examination of animals. New knowledge in rodent genetics has enabled dramatic growth in the number of human diseases emulated in genetically designed rodent models.

Rodent imaging helps bring new

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therapeutic drugs to market sooner and at reduced cost by providing more efficient pathways for preclinical evaluation of the therapies. These pathways include the following: Confirmation that a drug is delivered to and interacts with its intended target. Measurement of the pharmacokinetics, target efficiency, biodistribution, and elimination of the drug. Monitoring of these variables over time. Characterization of the target tissue. Identification of subpopulations of cells within the target that respond differently to the drug.

Rodent imaging also reduces the time and cost associated with evaluating nondrug therapies such as tumor ablation methods, radiation treatments, and genetic manipulation of tissues. Finally, technologies for rodent imaging can sometimes be upscaled to become improvements in imaging methods for humans.

New rodent imaging tools permit new queries to be made into fundamental biology, and answers to these queries often reveal a need for more imaging tools with which to pursue additional new knowledge. That is, new tools and new knowledge reinforce each other, leading to an ever-advancing frontier of new knowledge about human health and disease obtained through imaging research with rodents. Work at this frontier is multidisciplinary in scope, involving basic and computer scientists, engineers, mathematicians, and physicians working together and using rodent imaging tools to acquire new knowledge and advance the understanding of human health and disease.

### Research Challenges

Challenges to rodent imaging include the need for the following: Improved quantitative tools. Higher frame rates and throughput. Greater spatial, contrast, and temporal resolution. Improved registration of physiologic/molecular data with images. Higher sensitivity and reduced dose (when ionizing radiation is used). Standardized imaging protocols to facilitate multiinstitutional collaboration. Fast, simple, low-cost rodent imaging systems. Enhanced ability to distinguish drug effects from

imaging, anesthesia, and contrast agent effects. Improved instrumentation for rodent imaging, such as (a) high-frequency ultrasonographic (US) transducers, (b) multidetector, multisection computed tomography, (c) more sensitive x-ray systems that permit dose reduction to animals, (d) fast imaging systems to avoid anesthesia of rodents, (e) methods to acquire quantitative tissue information along with images, and (f) new imaging methods that avoid ionizing radiation.

### Conclusions

Rodent imaging is a young field and is far from mature. Equipment for rodent imaging is in its infancy, and many opportunities for improvement exist. Additional animal models for human disease are needed, especially for diseases other than cancer. A major handicap in the evolution of rodent imaging systems is the absence of a centralized source of interest in and funding of such systems—either in federal funding agencies or in industry.

### Imaging in Drug Development

The ultimate validation of a new therapy (drug) is a blinded, randomized controlled clinical trial in which symptoms, survival, and specific surrogate measures are compared between investigational and control patient groups. This is an essential final step in the validation and Food and Drug Administration approval process; however, it is exceptionally time consuming and expensive and is a highly inefficient method for eliminating ineffective drugs. Preliminary steps in which ineffective drugs could be eliminated before entering a large-scale clinical trial would accelerate the process and reduce the cost of bringing drugs to market, because personnel, patient, and financial resources could be devoted to just the promising drugs. Imaging has the potential to abbreviate the time and effort needed to accomplish this separation of more promising from less promising drugs.

### Research Opportunities

Imaging technologies that register images with associated quantitative physiologic,

molecular, and functional data can yield information about the ability of drugs to concentrate and effect changes in specific molecular targets based on time-varying drug uptake, distribution, and elimination computations. Creation of multiinstitutional databases of this information could facilitate the classification of patients according to their responsiveness to specific drugs. These databases also support multiinstitutional studies of drugs according to agreed-upon standardized study protocols. Identification of specific biomarkers that would be useful for evaluating drug effectiveness should be included in the protocols.

The use of imaging to delineate the drug delivery process and evaluate drug effectiveness is a multidisciplinary effort involving physicists, engineers, bioinformaticians, computer modelers, pharmacologists, physicians, and statisticians. Such coalitions require substantial cross training and an understanding of the language and expressions used by different groups, so that effective communication can occur.

### Research Challenges

Challenges to imaging in drug development include the need for the following: Identification of surrogate markers to aid in determining the distribution and effectiveness of specific drugs. Design of imaging technologies, including tracers and contrast agents, to facilitate development of drugs for specific patient subpopulations. Formation of a network of collaborative investigators from academia, industry, and government to accelerate bringing drugs to market. Development of protocols that reflect a consensus on (a) instrumentation to be deployed, (b) data-acquisition methods to be used, (c) quality assurance tools to be employed, (d) qualifications of independent observers, and (e) validated tools to be used for quantitative measurements.

### Conclusions

In the United States, the cost of bringing a new drug to market is approaching \$1 billion and requires several years of intense effort. Expediting the approval process and reducing the cost of drug

development is highly desirable to patients, health care providers, and payers alike. Imaging has the potential to improve the present situation. For imaging to be used most effectively in drug development, however, the molecular mechanisms of action of specific drugs must be better understood, so that the right drugs can be developed for the right targets and for the right diseases in the right patients.

### Imaging of Chronic Metabolic Disease: Diabetes

Type 2 diabetes mellitus is a debilitating and costly disease. Its prevalence is increasing dramatically in the United States and in several other developed countries. Currently, 21 million Americans suffer from diabetes and are at substantial risk for microvascular and macrovascular complications that heighten the risk of morbidity and mortality. Diabetes is a growing public health concern that needs improved methods for prevention, diagnosis, treatment, and follow-up. Imaging offers one promising tool to achieve these improvements.

### Research Opportunities

Imaging offers a noninvasive method to study the mechanisms and complications of diabetes in humans and in research animals that are genetically modified to express diabetes. Imaging of diabetic rodents reduces the cost, enhances the understanding, and expedites the discovery of improved methods of controlling diabetes in humans.

Diabetes assaults the cardiovascular system, and cardiovascular imaging is essential to understanding the biology and etiology of the disease. Imaging has the potential to assist in detecting diabetes early, monitoring the progression of the disease, assessing the effectiveness of control regimens, and identifying the appearance of major risk factors for life-threatening cardiovascular events. Imaging can be used to gain an improved understanding of diabetes by yielding a better model of the disease, with more explicit biomarkers for disease progres-

sion in organs and in the peripheral vasculature. Imaging to detect early diabetes in asymptomatic individuals could help to prevent or delay the onset of the debilitating effects of later-stage disease; speed the development of new therapies, with improved control measures; and reduce the associated risk of morbidity and mortality.

Diabetes is a metabolic disorder that challenges the basic knowledge of chemists, biologists, physicians, and behavioral scientists. A multidisciplinary team of these individuals is required, working with scientists, engineers, and bioinformaticians to improve imaging methods and with biochemists and pharmacologists to develop qualitative and quantitative biomarkers for disease progression and control in humans and animals.

### Research Challenges

Challenges in the imaging of diabetes include the need for the following: Greater understanding of the cause and consequences of diabetes, including its multifaceted impact on the cardiovascular system. Qualitative and quantitative biomarkers to monitor the control and progression of the disease in all stages. Better animal models for diabetes. A consortium for diabetes, similar to the mouse cancer consortium of the National Cancer Institute. Improved imaging methods at all scales, from molecular to whole animal to human. Multidisciplinary consortia of individuals interested in working collaboratively to better understand and control the diabetes epidemic in developed and developing countries. Imaging methods for humans that require no or minimal amounts of ionizing radiation so that they can be used on an ongoing basis to monitor disease progression and control.

### Conclusions

Diabetes should be declared an emerging health care crisis in the United States. Open forums should be established to discuss this problem, with participation of industry, academia, and federal and state agencies. An information-sharing network should be created that is dedicated to improvement of the prevention, early diagnosis, and treat-

ment of diabetes, as well as to improved methods to quantify treatment outcomes and reduce the morbidity of diabetes. New scientists should be encouraged to engage in diabetes research as one of the most challenging and intellectually fulfilling arenas of biomedical research.

### Image-guided Intervention in the 4th Dimension—Time

Image-guided intervention (IGI) is the use of biomedical images to guide medical interventions, including surgery, radiation oncology, and ablation therapy. With the exception of US and x-ray fluoroscopy, biomedical images are static and provide “snapshots” in time, rather than continuous images over time. This limitation presents difficulties for IGI in regions of the body where motion occurs. IGI in the 4th dimension (4D IGI) encompasses processes to quantify motion and delineate its impact on organ movement and deformation and provide motion-correcting algorithms to guide more accurate interventional procedures.

### Research Opportunities

Four-dimensional IGI is rapidly evolving, and its rate of development often outpaces the clinical validation of any particular approach. An ongoing network of collaborative research teams would help validation research keep pace with technologic evolution by expediting the clinical evaluation of a particular approach to motion quantification and correction; facilitating the collaboration among groups to improve research; and enhancing communication among research groups.

The objective of 4D IGI is safer and less invasive interventions that yield greater success. A successful therapeutic intervention is ultimately the removal or healing of diseased tissue, without damaging normal tissue to the degree that the patient's well-being is compromised. Another objective of 4D IGI is the development of real-time validation of treatment end points (biomarkers) to quantitatively assess patient outcomes and level of discomfort.

### Research Challenges

Challenges to 4D IGI include the need for the following: Improved multiparametric imaging that yields anatomic, physiologic, molecular, and functional information. Real-time tracking of motion and organ deformation. Automatic error-identification methods that detect misregistration and “loss of target.” Feedback mechanisms to automatically correct for misregistration and loss of target. Improved ergonomics of interventional suites to accommodate imaging equipment and improve patient access. Reduced radiation exposure to patients during 4D IGI techniques. A public-domain benchmarking database to facilitate research comparison and collaboration. Development of 4D IGI as an on-line, real-time process in the interventional suite. Identification of biomarkers for evaluating the success of 4D IGI.

### Conclusions

Four-dimensional IGI is highly technology dependent and requires a multidisciplinary team of scientists, engineers, and physicians working together to advance the technology and its applications. Technologies employed in 4D IGI are expensive, but the payoff is considerable in safer, less invasive, and more effective interventions. Research to improve 4D IGI is dependent on federal funding and requires the National Institutes of Health, in particular, to continue to expand its receptivity to grant applications that focus on technology development and are not premised on a biologic hypothesis. Industry and investors should also be pursued as potential funding sources for 4D IGI.

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