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Biomedical Imaging Research Opportunities Workshop III: A White Paper

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Abstract—The third Biomedical Imaging Research Opportunities Workshop (BIROW III) was held on March 11–12, 2005, in Bethesda, MD. The workshop addressed four areas of imaging that present opportunities for research and development: Multimodality Image-Guided Therapy, Imaging Informatics, Imaging Cell Trafficking, and Technology Improvement and Commercialization. The first three areas were individually addressed in their own plenary sessions, followed by audience discussions that explored research opportunities and challenges. This paper synthesizes these discussions into a strategy for future research directions in biomedical imaging.

Keywords— Image-guided therapy, Biomedical informatics, Cell trafficking, Imaging technology, Imaging research opportunities.

OVERVIEW

The third Biomedical Imaging Research Opportunities Workshop (BIROW III) was held on March 11–12, 2005, in Bethesda, MD. BIROW III was sponsored by the Academy of Radiology Research (ARR), American Association of Physicists in Medicine (AAPM), American Institute for Medical and Biological Engineering (AIMBE), Biomedical Engineering Society (BMES), and the Radiological Society of North America (RSNA). Nineteen other medical imaging societies participated in the planning and conduct of the meeting. The purpose of BIROW III (similar to the purposes of earlier BIROW meetings held in 2003 and 2004) was to identify and characterize opportunities for scientific research and engineering development in biomedical imaging. This paper presents the findings and recommendations of BIROW III.

BIROW III focused on four areas of imaging that present a wealth of opportunities for scientific research and engineering development. These areas are

- Multimodality Image-Guided Therapy,
- Imaging Informatics,
- Imaging Cell Trafficking, and
- Technology Improvement and Commercialization

By consensus of planners of BIROW III, the final topic is not included in this white paper because it differs in character and scope from the first three topics, and did not include a breakout session. Each of the first three topics was addressed in a plenary session in which experts in the field summarized the state-of-the-art science and presented a view of research opportunities. Each session was followed by an audience breakout session in which participants explored research opportunities and challenges. The plenary and breakout sessions yielded written reports that have been synthesized and edited into this paper. The various contributors are listed in the appendix. The finding and recommendations for these three areas of imaging are presented below.

MULTIMODALITY IMAGE-GUIDED THERAPY

Introduction

Image-guided therapy (IGT) denotes the acquisition and manipulation of biomedical images for active guidance of medical interventions. The expression "multimodality IGT" (mIGT) connotes the acquisition of images from more than one modality or form of imaging technology. IGT sometimes involves acquisition, processing and display of images in (near or actual) real time for active guidance of a therapy (e.g., a surgical intervention).[6,9,13,19,31] In other applications (e.g., IGT in cancer treatments with radiation over a 4- to 6-week period,) images may be obtained periodically to verify the placement of treatment fields and to monitor the progress of treatment.[10,17,25,32] Interventional procedures that employ IGT include surgery, radiation treatment, chemotherapy, intra-arterial catheter interventions, and thermal and freezing ablation techniques. Increasingly, imaging and treatment are becoming integrated so that imaging occurs during treatment, thereby improving the safety and effectiveness of the interventional process. Fan-beam CT and cone-beam CT units integrated

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into linear accelerators for cancer treatment are examples of combined imaging-treatment devices for radiation therapy.

Imaging studies have become more sophisticated through evolution of imaging technologies, and the integration of information from these studies is increasingly necessary. A significant amount of physician time is spent selecting and interpreting clinically indicated studies, assimilating information from different studies, and integrating this information into an assessment of the patient's clinical status. A rapidly evolving development is the incorporation of two modalities into one imaging system, to facilitate accurate spatial and temporal registration of information from two modalities into one set of images. Hybrid imaging systems available or under development include PET-CT, PET-SPECT, MRI-PET, MRI-US, US-PET, CT-US, Optical-US, US-X-ray mammography, and US-X-ray fluoroscopy.

Interdisciplinary, coordinated research is needed in mIGT. Specific opportunities for research include (1) selection and investigation of imaging combinations to be (a) developed as physical devices, (b) integrated to facilitate image registration and fusion, (c) matched to particular anatomic sites and diseases, and (d) tested in clinical trials; (2) evaluation of promising multimodality combinations of imaging methods; (3) development of software tools and algorithms for image registration, segmentation, and classification for combining and separating information; and (4) preparation of integrated platforms that (a) enable efficient clinical mIGT as a seamless process, (b) use common physical or software modules that provide a standard operational environment, and (c). accelerate clinical implementation of advanced imaging methods that promise to yield improved results. The variety of possible combinations of imaging systems and imaging/therapy systems is large. The financial and time costs of evaluating these combinations and their potential medical benefits are huge, if done haphazardly. An organized and logical process for this evaluation is mandatory.

State of the Art

Over the past decade, the number and capabilities of imaging modalities and their potential combinations have increased remarkably. Current imaging modalities used in IGT and mIGT include the following.

X- and γ-Rays

X-ray methods include radiography and fluoroscopy in single- and bi-planar operation, using analog (film, image intensifiers) or digital (direct and indirect conversion models) image receptors, computed tomography (CT) (multislice, helical), cone-beam (CT), electronic portal imaging devices (EPID) used at megavoltage (MV) energy levels, and MV-CT. Methods employing radioactive material include conventional γ-camera imaging, single-photon emission computed tomography (SPECT), and positron emission tomography (PET). Data acquisition modes include static, dynamic, and motion-gated for cardiac and respiratory cycles.

Ultrasound

Ultrasound (US) methods include surface, intra-catheter and trans-rectal orientations of two- or three-dimensional U.S. probes with single or multi-array geometries. Acquisition modes are typically dynamic, with rapid, real-time image production. Although US is typically used to identify anatomic boundaries, it can also be used in certain circumstances to characterize tissue properties through analysis of the reflected signal.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) includes T1- and T2-weighted, proton and multinuclear, spectroscopic, diffusion tensor, functional, and other imaging methods that are limited only by the design of relevant pulse sequences and by sufficient signal-to-noise ratios. The performance of MRI changes with field strength, and 3 T and higher units provide a capability not achievable at 1.5 T for many MRI applications. A small number of intra-operative MRI devices have been developed for real-time MRI-IGT.

Nonionizing Photons

Nonionizing photons are used for remote sensing and surface detection in the tracking of fiducial markers, microwave tomography, laser tomography, and for molecular imaging using techniques such as bioluminescence, phase-contrast imaging, and optical coherent tomography.

Criteria to Validate Opportunities for mIGT Research

The breakout discussion session focused, in part, on identifying criteria to validate opportunities for mIGT research. The four criteria identified are derived in part from the NIH Roadmap.[39]

Criterion 1—Deepen Understanding of Biology

mIGT may permit targeted energy deposition in tissue with such precision that the responses of normal and abnormal tissues can be examined in great detail. To achieve this objective, mIGT must provide quality multimodality images with accurate spatial and temporal localization, and dependable physiological, functional, metabolic, biochemical, and molecular information. Already, image-guided radiation therapy (IGRT) is permitting delivery of higher radiation doses to tumors and lower radiation doses to normal tissues, thereby enhancing the likelihood of effective

treatment without disastrous side effects. Further, radiation toxicity assessment scores and knowledge of physical dose distributions in patients are providing insight into fundamental biological processes associated with cancer and its treatment. mIGT, selectively targeted radiation and chemical agents, and molecular imaging are expanding the frontiers of biological knowledge. Without question, mIGT is contributing substantially to a deeper understanding of biology.

Criterion 2—Stimulate Interdisciplinary Teams to Move Fundamental Developments into the Clinic

mIGT is intrinsically interdisciplinary. Three drivers of medical advances are technology, molecular biology, and pharmaceuticals, and mIGT is strongly influenced by each. Experts in each of the areas are required for (1) developing and testing mIGT, (2) applying multimodality image guidance to the study of basic biological processes and the evolution of more effective treatments of disease, and (3) applying and evaluating these advances in the clinic. Persons contributing to mIGT research include basic scientists in physics, chemistry, biology, genetics, physiology, pharmacology, mathematics, and computer science; engineers in biomedical, mechanical, electrical, process engineering, and operations research; and clinical scientists in radiology, radiation oncology, internal medicine, cardiology, and the surgical subspecialties. Interdisciplinary teams must be present in industry, academia, and clinical settings to facilitate the development, evaluation, and deployment of mIGT in the clinical environment. Because of the multivariate complexity of mIGT and its use in humans, all facets of the approach must be critically optimized and validated along the entire pathway from conceptualization to clinical deployment. To satisfy this requirement, interdisciplinary teams of basic scientists, engineers, and clinician-scientists are essential.

Criterion 3—Accelerate Medical Discovery

Continued development of mIGT will accelerate medical discovery in biology and in technology and pharmaceutical development. Tools to handle image-guided interventions, such as devices for precise positioning and image registration and software for precise alignment of tissues for treatment, will advance interventional approaches such as microsurgery, robotic surgery, and precision radiation therapy. mIGT assists now in the screening of new pharmaceuticals and assessment of chemical, molecular, cellular, and ablative therapies. Novel contrast agents are needed for use with various imaging modalities, to permit noninvasive characterization of normal and diseased tissues, and targeting abnormal cells for deletion by micro- and nano-technologies. New approaches for imaging temperature distributions, apoptosis following cytotoxic therapy, and populations of hypoxic and proliferating cells are examples of mIGT's continuing contributions to the acceleration of medical discovery.

Criterion 4—Improve Health

mIGT contributes significantly to the delivery of spatially and temporally optimized interventions that move medicine closer to its mission to cure disease without harm to patients. Treatments are delivered with greater accuracy and precision, and normal tissues are spared to a greater degree. As a consequence, the quality of life is enhanced and the morbidity of treatment is reduced. mIGT used with novel imaging technologies promises to improve human health through individualized medicine. For example, nanoparticle-loaded T cells concentrate in different parts of a tumor at different times during therapy, opening new possibilities for tailoring treatments for individual patients. Further, clinical efficacy of treatment can be assessed through surrogate measures, rather than waiting for months or years, to see if the treatment fails. mIGT has a superb potential to improve human health through noninvasively directing interventional processes and then monitoring the effect of the processes.

Challenges to Further mIGT Development

The promise of mIGT to improve disease treatments and expand the understanding of biological processes is stunning. However, imaging technologies are expensive and require the knowledge of interdisciplinary teams in their evolution and deployment. Validation and verification continue to be a challenge to deployment of mIGT. Investigation of image signatures (tissue characterization) is being explored, and image-based surrogate measures for normal and abnormal tissues are needed.

There are many challenges related to scale—spatial, temporal, and number of signal acquisitions (concentration)—that must be resolved in the translation of imaging data acquired with animals to humans. These challenges are formidable, but they must be overcome if the full advantages of mIGT are to be realized.

Informatics issues in mIGT are equally formidable.[7,38] Imaging systems today can generate far more information than can be assimilated by the human observer. How this information is managed, selected, and presented to the physician for interpretation is a dilemma that requires enhanced knowledge of how the human mind assimilates and interprets information, as well as improved technologies for the management of imaging information.

Recommendations in Support of mIGT

A continuously evolving strategic plan is needed for research and development of various imaging modalities and their combined roles in mIGT. The number and

combination of modalities with potential for mIGT is growing, and the cost of research and development could easily escalate beyond what is affordable if a plan to rationally select modalities and combinations of modalities for potential mIGT is not developed. The plan must be dynamic so that realistic opportunities for mIGT are pursued and unrealistic proposals are rejected. Experiments using separate modalities can help guide the decision to develop an mIGT system that combines the modalities. Improved image registration and segmentation algorithms, and other software tools, are needed that are robust, accurate, and fast enough for real-time use.

The clinical impact of approaches to mIGT should be evaluated in stages, initially using comparisons with current standards of care and evaluations employing intermediate indicators of efficacy. At some point, before launching well-designed clinical trials that examine the impact of mIGT on long-term survival and quality of life, reimbursement of mIGT should be available to expand the evaluative process to include the typical clinical environment. The process of evaluating clinical impact should involve research institutions, industry, scientific organizations, and government agencies in a collaborative endeavor to improve health care in the most cost-effective manner possible.

Well-designed and controlled clinical trials are needed to evaluate multimodality imaging and clinical decision trees. Trials that simply compare one imaging parameter with another are inadequate. The true incremental benefit obtained by adding various imaging modalities together must be quantified, and surrogate measures are needed that yield quantitative indices over a short time period. Protocols are needed that use statistical and operations analysis to identify which combinations of imaging techniques provide the most useful information within a reasonable time and for a reasonable cost.

Multidisciplinary training of engineers and basic and clinical scientists must be expanded. Students from various disciplines should be brought together in order to understand each other's strengths and weaknesses. Imaging physicians and scientists should be educated in advanced biology and biochemistry, and biological scientists should have an in-depth education in imaging science and engineering.

The availability of targeted agents for imaging is a potential limitation in mIGT. For example, the availability of radionuclides for research and clinical application is currently threatened by proposed major reductions in research funding in the U.S. Department of Energy.

A current technological shortcoming is the shortage of three-dimensional position-sensing devices that are accurate, lightweight, and robust enough for free-hand tracking of imaging and therapy equipment.[37] Multimodality systems for guiding therapy are complex, and accurate feedback to the users is essential. Also necessary is in-depth education to ensure that users understand the feedback and can make decisions that ensure effective and safe applications of mIGT in the clinical environment. Some mIGT systems operate in real time, and place even greater demands on the speed by which data must be managed and decisions must be made by the user.

mIGT systems to be used with small animals (mice and rats) are recent innovations, and their design should continue to evolve together with reductions in cost. These systems are useful in their own right in molecular imaging, and also serve as small-scale prototypes for clinical multimodality instrumentation.

Decision systems and guidance and control technologies are key in modern imaging systems, and are even more critical and complex when multiple imaging modes are combined with a therapeutic system. Operations management, process control research, and out-of-the-box conceptualization and design can be used to address the complexity, reliability, and operator use of such systems.

Definitive standards are needed for image-data exchange, classification, and validation of imaging systems for treatment guidance and assessment. Statistical algorithms and clinical-trial designs should be developed to better evaluate improvements offered by novel approaches to mIGT. Also, bioinformatics and image-processing methods are needed to accelerate rapid use of the massive quantities of data gathered before, during, and after mIGT-controlled treatments.

New approaches are needed in the regulation of multimodality imaging agents. The U.S. Food and Drug Administration (FDA) should not be expected to ensure the safety and efficacy of imaging agents, but should instead provide approval based on judgments of risk and benefit of the agents. When used in small amounts to plan, guide, and assess response to treatment, the requirements for safety and efficacy should be weighed against the risks of not having this guidance.

Innovative approaches to clinical trials that mine large mIGT datasets are needed—the customary approach of evaluating a drug with simplistic binary endpoints is grossly inadequate. The greatest amount of data possible should be acquired from each patient involved in an mIGT trial, to permit extraction of information with the greatest predictive value. Currently, institutional and agency restrictions are overly conservative when applied to mIGT with various imaging agents. These restrictions, including those of the FDA, should be loosened when applied to systems and agents used for evaluating therapeutic interventions in which the systems and agents are orders of magnitude less risky than the disease that is being treated.

Conclusions

mIGT contributes to therapeutic interventions at several levels, including screening, diagnosis, localization, staging, guiding, tracking, and postintervention evaluation. There

are several obstacles to overcome in performing efficient clinical trials of mIGT procedures, including an intrinsic bias in favor of binary clinical trials. For mIGT, large-scale trials that generate large amounts of multiparameter data are necessary, and require new approaches to regulation that facilitate the development and evaluation of innovative imaging agents and combinations of imaging modalities. Research in mIGT is an interdisciplinary process that demands insightful basic scientists, engineers, and clinical scientists working together in collaborative teams. Medical, graduate, and postdoctoral educational programs that reflect this interdisciplinary, collaborative framework are essential. Without question, mIGT

- contributes to the understanding of fundamental biology through more accurate and precise image-based targeting and delivery of therapeutic interventions, and effective post-treatment evaluations;
- requires and stimulates the education and training of interdisciplinary teams, both in research and in clinical applications;
- accelerates medical discovery through interdisciplinary processes that span both basic and clinical science; and
- contributes to the well-being of patients through more accurate and precise interventions that are based on a higher level of understanding of biological processes intrinsic to normal and diseased tissues.

IMAGING INFORMATICS

Introduction

Medical informatics has been defined as "a field of study concerned with the broad issues in the management and use of biomedical information, including medical computing and the study of the nature of medical information."[22] This definition fails to capture the scope of imaging informatics, which encompasses every aspect of imaging from scheduling to data acquisition to interpretation to reporting to archiving to retrieval. Imaging informatics is essential to the practice of biomedical imaging, and is the focus of a new profession that focuses on developing innovative tools for research and new algorithms for harmonizing large quantities of imaging data of interest to multiple medical disciplines.

The professional role of the imaging informaticist fills a knowledge void in imaging, and forms a bridge within imaging and between imaging and other medical disciplines. In the past, information technologists and systems analysts were consulted on an *ad hoc* basis to provide technical advice when needed; typically, however, these individuals were unaware of the specific needs of biomedical imaging and its research and clinical goals. In a few institutions, physicians and physicists acquired some of the specialized knowledge needed to interface productively with the consultants, but in most institutions the level of communication between imagers and information specialists was flawed. This dilemma has stimulated the development of imaging informaticists who can transcend the boundaries of organ systems and different modalities and make the necessary connections among radiologists, physicists, technologists, and information specialists. This development is creating a new discipline that demands substantial clinical knowledge, a solid grounding in digital imaging technologies, a substantial quota of diplomacy and interpersonal skills, and a dedication to the notion that change is a characteristic—not an option—in modern imaging.

State of the Art

Imaging informatics is essential to techniques such as decision support, structured reporting, and artificial intelligence as they are applied to the interpretation of biomedical images.[20] Each of these strategies is important to acquisition of "just-in-time" knowledge in support of the interpretive process in order to (1) improve the accuracy and timeliness of interpretations in a climate of escalating workloads; (2) integrate imaging more closely within the larger healthcare enterprise; and (3) improve the contribution of biomedical imaging to detection, diagnosis, and therapy in order to enhance patient outcomes and research efforts. In the "just- in-time" approach to knowledge acquisition, digital imaging results are mined to create new stores of knowledge that are machine-readable, reusable, and available to be analyzed and studied in support of evidence-based medicine.

Digital imaging is forcing the "reinvention" of the traditional film-based reading room. This transition is far more fundamental than simply a cosmetic trading of light boxes for computer monitors. Instead, the role of the radiologist is changing from passive to active, with a host of navigation, manipulation, communication, and decision support tools available to aid the interpretive process. Simultaneously, the number of images to be interpreted is growing exponentially with the advent of new technologies such as multi-slice CT and hybrid imaging modalities that fuse anatomic and physiologic data. Guidelines and standards are needed to help guide this growth in technology and workload and its influence within the digitally based department.[15] As imaging informatics continues to evolve, increased interplay will be needed among engineers, physicists, mathematicians, psychologists, clinicians, and others to ensure that medicine manages the evolution of technology rather than the other way around.

Challenges to Imaging Informatics Development

Imaging informatics is staffed today almost exclusively by individuals who are trained specialists in other fields (radiology, physics, engineering, computer science) and

who have taken an interest in working at the intersection of digital imaging and information technology. The field remains indistinct—few avenues of formal education exist, and those that do exist vary widely in focus, curriculum, and clinical experience.[23] Most informatics programs accentuate the operational aspects of imaging at the picture-archiving and communications systems (PACS) and workstation levels, and pay inadequate attention to overall workflow in the healthcare enterprise, interoperability of information systems among institutions, meta-data scaling, or integration of informatics research and analysis into the clinical setting.

Although the physical environment for image interpretation is changing dramatically, little effort has been directed to encouraging receptivity to research within the workstation, reading room, or departmental environment. Potential opportunities exist, such as the Insight Toolkit (ITK), an open source, public software platform being designed by the National Library of Medicine for support of imaging research in segmentation, classification, and rigid deformable registration techniques for processing multidimensional medical data.[1] ITK employs leading-edge segmentation and registration algorithms in two to four dimensions. ITK can be configured with standardized auditing tools, dedicated research workstations, and other innovations to create research opportunities within the image-interpretation environment.

The number of industry participants in the imaging informatics marketplace continues to expand, with a disorienting range of new tools, technologies, software, and applications available. Several user groups have worked collaboratively with vendors over the last decade, and these efforts have yielded short-term changes to specific products. Although the longer-term need for standards in image quality and exchange has been acknowledged, no formal plan has evolved for uniform protocols or methods to assess the quality of data from new imaging technologies in a common language. The absence of these standards creates confusion about the interoperability of products, new purchase decisions, and potential options that leverage optimal use of personnel and machine resources. This confusion causes administrators and imaging specialists to be apprehensive about embracing new informatics technologies.

The lack of standards for acquiring, reconstructing, viewing, manipulating, transmitting, and retrieving of biomedical images needs to be addressed by research and the development of guidelines through a consensus process. This challenge fits within the larger framework of the U.S. Department of Health and Human Services mandate to create a seamless electronic medical record for all U.S. residents that can be accessed anytime and anywhere. There are several obstacles to meeting this challenge, including the reliability of shared imaging data across institutions, variability in data acquisition techniques and reconstruction algorithms among vendors, and inconsistencies in the imaging lexicon that make intercomparisons among institutions difficult, even when images are acquired as part of a federally or industry sponsored clinical trial.

No operational framework exists to encourage imaging specialists to integrate research into the clinical workstation or reading-room environment. Few radiology departments have research-grade computer programmers and most do not insist on open-architecture software (which many vendors are reluctant to provide). As a consequence, departmentally based research in biomedical imaging is handicapped, because each research project is confined to the code of its own imaging platform, and the results are not translatable across platforms. This handicap is a serious barrier to achievement of the ultimate goal of a national platform for open-access research in biomedical imaging in order to advance the frontiers of the imaging enterprise.

Few educational tools and training devices have been developed to bring radiologists, other clinicians, physicists, and others up to speed on the optimal design and use of new digital imaging technologies. Training is machine-specific, provided as part of user orientation, and focused primarily on clinical applications rather than the underlying physics, engineering, and biological principles. This training is usually vendor-specific, and often becomes rapidly outdated as technological features of equipment are exchanged for new ones.

Imaging informatics has not yet been incorporated into the research emphases of the National Institutes of Health (NIH). Because of its traditional focus on diseases and organ systems, the NIH has had a difficult time finding a place for imaging informatics, although the recently founded National Institute of Biomedical Imaging and Bioengineering (NIBIB) is attempting to rectify this shortcoming. Despite the urgent need for assessment of interchangeability and comparability of imaging contributions to clinical trials, few imaging informaticists sit on NIH research review committees.

Recommendations in Support of Imaging Informatics

Recommendations generated during the discussion of image informatics are listed as follows.

- Image informatics educational programs are needed to create new specialists and provide continuing education for those working in the field.[14] These programs should be thoughtfully and formally developed, and not be simply an *ad hoc* compilation of courses appropriated from existing disciplines such as electrical engineering and computer science.
- A conduit into clinical practice should be established for the Insight Toolkit and other robust software tools as pluggable modules into imaging workstations. This conduit should be developed by

informaticists, clinicians, and vendor representatives.

- Professional organizations should work together to develop tools and techniques to improve the quality of new technologies for imaging informatics. This work should focus on open-source collaboration, accelerated mechanisms for stress-testing of imaging technologies, venues for publication of results of these tests, and research on simulators of integrated systems that can predict the utility of new technologies in specific operating environments.
- Standards should be developed to facilitate interoperability of imaging technologies. Industry representatives, clinicians, and innovators should work together to develop standards and provide an interchange platform to facilitate communication across datasets and to integrate research findings into clinical practice. An interchange platform would enhance the participation of imaging specialists in clinical trials, and permit expansion of trials to accommodate patients from previously untapped populations outside academic medical centers.
- Programs should be developed to train healthcare professionals in the routine use of imaging informatics, and to encourage incorporation of codified best practices into their practices.
- Informaticists should sit on NIH research review committees. These individuals should inquire about the integrity and interchangeability of imaging data among research sites in multi-site clinical trials. Further, a "universal" architecture should be developed at the NIH that can capture and archive images and supporting studies from such trials to create a reservoir of research information that could be useful to investigators nationwide.

Conclusions and the NIH Roadmap Initiative

The NIH Roadmap is an integrated vision designed to deepen understanding of biology, stimulate interdisciplinary research, and reshape clinical research to accelerate medical discovery and improve health.[39] Imaging informatics has the potential to help advance each of these Roadmap themes:

- *New Pathways to Discovery:* Imaging informatics has the potential not only to contribute to research efforts across the spectrum of NIH-supported clinical trials, but also to create avenues into heretofore inaccessible reservoirs of retrospective imaging data. By identifying ways in which image acquisition, processing, and display can be harmonized, working toward construction of a unified language to describe imaging results, and participating at all levels in the creation of a seamless electronic medical record available nationwide, imaging informaticists will help create a widely accessible and comparable database of medical images that can accelerate new discoveries in disease prevention, diagnosis, and treatment.
- *Research Teams of the Future:* The medical informaticist serves as a logical starting point from which biomedical research teams of the future can develop. Uniting disciplines, spanning knowledge bases, and applying tools that cement research and clinical practice, the informaticist will be a key individual in research collaborations and healthcare delivery teams. Creation of a dedicated discipline of imaging informatics specialists should provide a template and a body of positive outcomes experience on which other medical disciplines can shape the creation and integration of informatics team members into their activities.
- *Re-Engineering the Clinical Research Enterprise:* By integrating research into routine clinical activities, introducing data mining and aggregation techniques, and working to relate knowledge gained in one discipline with that from others, imaging informaticists are fulfilling the promise of raising clinical research to new levels.

IMAGING CELL TRAFFICKING

Introduction

Loading cells with a traceable label and following their fate *in vivo*, a technique known as cell trafficking, provides useful information in support of two major objectives: cell-based transplantation medicine (stem cells, lymphocytes, platelets, etc.), and basic biological research. Development of cell-trafficking techniques requires a deep understanding of biology and an interdisciplinary approach to research involving biologists, chemists, engineers, and physicists.

State of the Art

Cell-based therapies have great potential to improve treatment of a wide range of disorders, including neurodegenerative diseases (Alzheimer's, Parkinson's, multiple sclerosis),[27,29,31] spinal cord injury,[28] liver and kidney disease,[12,16] repair of ischemia-related cardiac and brain damage,[35] joint disease,[3] diabetes,[33] and treatment of malignancy.[4] The ability to track the location and functionality of cells offers the opportunity to shape clinical research, because the performance of transplanted cells (targeting, retention, degree of cell differentiation, and the role of the extracellular matrix) is not well understood.

Cell trafficking in embryo models provides simple *in vivo* systems to study cell differentiation pathways and to

understand how aberrant events lead to disease.[18] Supplying, or stimulating the formation of new cells that can repair defects caused by failing cells is encouraging researchers in developmental biology to employ cell-tracking methods similar to those used in clinical studies. In these and other applications, dynamic imaging methods are important to understanding how cells behave in native and new environments. Optical imaging methods are ideal for many of these studies, and contribute to the foundation for translational studies that build upon basic research.

Methods of cell loading and tracking employ radioactive, magnetic, optical, acoustic, or genetic labels in conjunction with an appropriate imaging modality.[34] Each method has specific advantages and disadvantages. As an example, several techniques have been developed to visualize and track cells over time in the injured myocardium.[36] One method uses magnetic resonance imaging (MRI) to track cells loaded with iron oxide.[21] This method provides little information on the quantitative distribution of labeled cells, however, because intensity changes in the MRI signal cannot be related *in vivo* to concentration differences of contrast agent. This approach also provides little information on the differentiation or functionality of the labeled cells.

Dextran-coated superparamagnetic iron (SPIO) nanoparticles are used for MRI imaging of hepatic reticuloendothelial cells.[11] The SPIO nanoparticles are biodegradable—they are metabolized and the iron is placed in the normal iron pool for incorporation into hemoglobin or for other metabolic processes. Various approaches have been developed to magnetically label stem cells and other mammalian cells using commercially available FDA-approved nanoparticles, or nanoparticles custom-synthesized with alterations in the Dextran coat or through the addition of proteins, antibodies, or ligands on the surface. Preliminary work with these cells indicates that the nanoparticles appear to be sequestered in endosomes within the cytoplasm of the cells, and that the SPIO nanoparticles do not influence long-term cell viability, proliferation, rate of induction of apoptosis, or formation of reactive oxygen species.[2] Following labeling with SPIO in culture, stem cells differentiate along desired lineages depending on cytokines added to the medium, so long as the preparation is clean and does not add significant numbers of nanoparticles to the medium. Labeled cells respond to cytokine and antigen stimulation, and magnetically labeled cells introduced intravenously or into tissue home to pathology sites. By using liposomes to deliver the label to cells, a reduced amount of label can be used and cell viability, proliferation, and differentiation capacity can be preserved.[36]

The imaging of genetically modified cells, such as thymidine-kinase-expressing cells imaged with PET and green fluorescent protein (GFP)-expressing or luciferase-expressing cells imaged with optical techniques, provides a method to track cells through many cell divisions over substantial time periods. Optical imaging methods are widely accessible and provide rapid, high throughput information from animal studies.[5] Although important in animal research, the use of genetically modified cells for cell tracking in patients is probably unlikely in the foreseeable future, especially in light of recent safety concerns surrounding gene therapy protocols.

SPECT imaging of cells labeled with ^{111}In-oxine or ^{99m}Tc is gaining acceptance in cardiovascular and inflammation studies, and could have broader application to general cell trafficking investigations.[26] PET is gaining widespread clinical utilization, especially in combination with CT and MRI. PET provides accurate quantitative studies of uptake, and yields sensitivities in the nano- to pico-molar range. Cells can be radiolabeled by radioactive antibodies, *in vitro* with a lipophilic agent such as ^{64}Cu-PTSM (pyruvaldehyde-bis(N^4-methylthiosemicarbazone)),[30] or by a PET reporter probe such as ganciclovir or a penciclovir analog. SPECT and PET can provide estimates of cell retention and biodistribution over periods up to a week, depending on the radiolabeling method employed and the half life of the isotope. Reporter probes permit follow-up studies for as long as the reporter genes are expressed.

Ultrasound contrast agents are phagocytosed by leukocytes, and can be used to detect regions of increased cell density.[8,24] Although ultrasound does not reveal the whole-body distribution of labeled cells, assessment of the location of the cells in cardiovascular and other tissues may be helpful.

Challenges to Cell Trafficking

Imaging and tracking cells are techniques that are bridge basic and clinical research, and support in both the areas is needed. Cell loading and trafficking methods are essential to advances in clinical medicine and in basic research, especially in developmental biology. For therapies at the cellular level to become a clinical reality, their benefits must outweigh their risks. One risk is the possibility that cells may migrate to, and persist in, nontarget sites where they may cause a detrimental outcome. Without effective cell-tracking methods, this risk may be unrecognized, and the development of methods to optimize cell homing to specific sites may be impeded.

Cell labeling provides important mechanistic insights for the cell transplantation field. Identifying relationships between transplanted cells and positive functional outcomes is essential to migration of cell therapy into the clinic. In the cardiovascular field, positive preclinical outcomes are being obtained with cell therapy without verification of cell presence in the affected tissues. It is not clear whether this reflects a possible noncellular (paracrine) effect that can be obtained without cells, or simply an inability to track cells *in vivo*. This issue can be resolved only through use of high-fidelity cell labeling and tracking techniques.

The development of methods to establish that labeled cells maintain normal function is critical. Assays of cell function have been developed for stem cells, because these cells are used in transplantation medicine and gene therapy. These assays are the exception rather than the rule, however. In some cases, there is no consensus on which assays for cell function and concentration should be used, and there are few standardized protocols. Finally, the long-term stability of contrast agents must be determined, and their potential toxicity characterized.

There are important issues to be resolved, concerning the clearance of contrast agents from tissues. These issues include whether the agent is present intracellularly or extracellularly following cell death, whether the released agent is incorporated into resident tissue macrophages or other cells, and how tissues clear the contrast agent. There is no consensus on how these issues should be resolved, and few protocols to guide investigations.

A major challenge is to quantify how well results obtained in a culture dish under ideal conditions translate to the clinical environment and remain effective *in vivo* over reasonable treatment periods. The evaluation of labeled cell function in experimental models may or may not mimic the conditions encountered in the human under disease conditions. Early translational studies are important to evaluate the clinical relevance of techniques for cell therapy.

Recommendations in Support of Cell Trafficking

If research into tracking stem cells is to be supported, then support must also be forthcoming for stem-cell research. Limitations in stem-cell research support, and the paucity of cell lines available, are obstacles to the development of effective cell trafficking methods. Support for stem cell research, research into tracking stem cells loaded with imaging probes, and research on imaging methods for stem-cell therapies is essential if the field of cell trafficking is to realize its vast clinical potential.

A second obstacle is the limited number of individuals and interdisciplinary teams trained to address all aspects of this challenging problem. Enhanced cross-disciplinary educational opportunities in cell-based transplantation medicine, probe chemistry, and imaging methodologies are sorely needed.

Instrumentation is lacking for precise quantification of cell distribution, concentration, and functionality—especially in small-animal models. MicroPET, microCT, SPECT, and large-field magnets for magnetic resonance studies are expensive to purchase and maintain, and many institutions are inadequately equipped to contribute to cell-therapy research. This deficit must be addressed if cell therapy is to move efficiently from the bench to the bedside.

Safe multimodality probes and imaging instrumentation and protocols are needed for cell-trafficking studies. This need encompasses both multimodality imaging techniques (e.g., CT/PET) that use two imaging methods and a single modality probe (radiolabeled cells), and multimodality imaging methods that measure multiple labels on a multimodality probe.

Many cells under consideration for transplantation (e.g., stem cells derived from blood or bone marrow) require little manipulation *in vitro*, and can move from harvest to implantation in a few hours or less. If labeling is to be incorporated into this process, it must be quick and efficient. Developing labels that are retained and whose impact can be evaluated in real time will be important for these cell types.

A major impediment to stem-cell therapy is the lack of markers to identify stem cells derived from preclinical species other than rodents. Development of high-fidelity, nongenetic labels (preferably with fidelity similar to the genetic labels available with rodents) that can be used to track cell populations *in vivo* would be a major advance in the field of cell labeling and tracking.

A dialog should be developed between the scientific community and regulatory agencies concerning the requirements for cell trafficking in the clinical environment. Designing reasonable standards for probes used in cell labeling and handling, and for maintenance of cell function after loading, present major new challenges to the scientific and regulatory communities that are unlike those for current biologicals, drugs, and devices.

Conclusions

While progress has been substantial in the development of new cell-trafficking technologies and applications, an additional research commitment is required to move this progress into clinically based regenerative medicine. With the vast potential of this field to alleviate human disease and suffering, a major commitment to funding basic and translational research in cell trafficking should be made.

APPENDIX

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