Session 3: Basic Research Issues

Participants in the Basic Research Issues session and the breakout discussion that followed focused on the exciting research currently underway in molecular imaging and on the trends and challenges likely to be encountered in the near future.

David Geho, MD, PhD, began the session with a presentation on oncogene cell differentiation and cell transduction. He noted that "from the perspective of molecular imaging and pathologic diagnosis, the transition from primarily a morphologic assessment into a detailed, real-time molecular diagnosis for each patient would represent a quantum leap in patient care," enabling "molecular description of disease at an early stage, before it is detectable by a physical exam and when it would be more easily treated." He presented an overview of current work and of the additional research that will be necessary to make individual molecular tissue profiling of patients a clinical reality.

Michael J. Welch, PhD, reviewed recent trends in radionuclide-based molecular imaging, including the reasons behind the primacy of ^{18}F-FDG PET in current applications. He identified several barriers to the translation of new agents into clinical use, including questions of intellectual property ownership, the commercial potential for novel radiopharmaceuticals, and regulatory difficulties in securing approval.

The role of MR in molecular imaging was presented by John C. Gore, PhD, who provided an overview of current uses and topical issues. He also reviewed the current uses of MR contrast agents as nonspecific contrast, targeted agents, "smart" agents (that change their efficacy in response to specific chemical processes), and cell labels.

Lihong V. Wang, PhD, provided perspectives on the current state of research in high-resolution optical imaging, including limitations and likely avenues of new exploration.

The final presenter in the session was Malcolm J. Avison, PhD, who reviewed radiologic approaches to molecular imaging, including the role of CT. He addressed the central question in integrating radiologic approaches into basic research in imaging: "What are reasonable expectations for the achievable sensitivity of detecting molecular imaging agents using x-ray methods at acceptable radiation doses in animal models and in the clinical setting?"

These broad overviews of research in molecular imaging were followed by a lively discussion session in which the participants identified a number of trends and challenges and developed several consensus recommendations.

Discussion: Trends and Challenges

Participants in the Basic Research Issues breakout discussion session began by identifying scientific and organizational trends and went on to address current challenges to advancement. Consensus recommendations were created on the basis of these discussions. Among the areas of specific focus were the new drug approval process, improved radiochemistry methodologies, and education and training.

The expensive, lengthy, and often disappointing process for approval of novel radiotracer or radiolabeled therapeutic agents was discussed in some detail, and a number of significant barriers were identified. Among these are what are perceived as unreasonable and sometimes scientifically invalid requirements and questions from the U.S. Food and Drug Administration (FDA). An area of great interest to participants was the question of knowledge transfer and cooperation in drug development between academic institutions and industry. Some universities have experienced difficulties in patenting imaging agents or in clearly identifying and protecting the intellectual property (IP) associated with drug discovery. IP, as session chair Welch noted, is the "key to commercialization," yet is often poorly understood. Moreover, participants noted a widespread academic aversion to the entire process of taking a drug from the laboratory to clinical use, a path that is sometimes viewed as offering more challenges than rewards. The academic recognition accorded to those who succeed in seeing a drug through from discovery to clinical use is limited. Although some efforts, such as the National Cancer Institute Development of Clinical Imaging Drugs and Enhancers (DCIDE) Program, have been designed to assist academic and business investigators in the IND process, participation in such efforts often presents its own challenges. In addition, the DCIDE program does not cover therapeutic agents. Industry faces equally daunting hurdles, with high development costs, short patent duration, and, sometimes, unclear IP positions. A key question that emerged from the discussion was whether a new paradigm is needed for the approval of molecular imaging agents for use in humans.

Another group consensus was on the need for novel approaches to radiochemistry education and training at the undergraduate and graduate levels as well as in medical schools. One urgent need, both now and in the future, is for trained chemists who understand the principles of designing contrast agents for the wide range of molecular imaging modalities. These individuals should be trained in part as medicinal chemists with skills in organic synthesis but should also have formal training in molecular and cellular biology to understand how contrast agents behave in cells and in vivo. Imaging instrumentation would be a valuable part of training coursework.

Increasing the number of trainees and the quality of their preparation will undoubtedly help to address some of the problems in improving radiochemistry, including current low and variable yields (particularly for ^{18}F compounds) which, although suitable for initial animal/human studies, are too low for commercialization. Research on improved yields with the submission of process patents for new technologies is needed.

A number of basic science challenges were addressed on various aspects of pharmaceutical development. In the area of radionuclide therapy, these challenges included the need for more sophisticated methodologies to assess the effects of targeted radiotherapies (including considerations of the biological bystander effect and tissue heterogeneity) and identification of serum biomarkers that reflect the effects of radiation on both tumors and normal tissues.

In the area of optical imaging, a number of near-term needs were identified, including more probes that can be used for high-resolution photoacoustic imaging and large absorption cross-sections that peak around the 800-nm near-infrared wavelength to attain deep penetration (several centimeters). It was agreed that optical imaging was an area that merits substantial additional attention from the molecular imaging community as refinements in technique and instrumentation continue.

A lengthy discussion addressed the development of contrast agents for radiofrequency molecular imaging and the general utility of CT, US, and MR as molecular imaging modalities. The group noted that technological advances in scanner design and associated improvements in sensitivity suggest that some of the traditionally "less sensitive" modalities should be revisited. High-resolution radiofrequency-induced thermoacoustic tomography, for example, can provide radiofrequency contrast and ultrasonic resolution. Specific developments to be expected in the short term from MR/CT, MR/MR spectroscopy, ultrasound, and optical imaging were listed and discussed.

One difficulty that must be addressed if bench-to-bedside efforts are to be successful is identifying patients who need molecular imaging studies. A large proportion of the patients who might benefit most from molecular imaging are presymptomatic. Given the fact that the entire population cannot be screened using molecular imaging modalities, how can these presymptomatic patients be identified? The answer lies in the identification of new serum screening biomarkers that can preselect patients for early molecular imaging. In the future, an annual serum screen for a broad range of disease possibilities may be a standard of care. Such a procedure would not only identify candidates for molecular imaging but could identify additional targets for molecular imaging agent development as well.

The challenges associated with validation of surrogate markers were addressed in some detail in the breakout session, including the different meanings associated with "validation," depending on the scientific or regulatory community served. One consensus of the group was that more sophistication is needed in preclinical validation, including clear delineation of requirements for preclinical and clinical validation. Key questions included:

- How can the types of validation studies performed in animals be effectively transitioned to humans?
- How can patients be encouraged to participate in the complex protocols required for some surrogate marker validation studies?
- How does one approximate/approach what has previously been relied upon (e.g., blood pressure) as a marker for response?
- When proposing an imaging agent as a surrogate marker for a drug's effectiveness, how does one convince clinicians that the surrogate is doing what it is supposed to do?
- Who, in fact, should the molecular imaging scientist be trying to convince: industry, clinicians, or regulatory agencies?

Recommendations

Participants in the discussion session made several recommendations for action. Among these were recommendations to:

- Encourage the SNM, perhaps in partnership with industry, to increase the number of fellowships and grants awarded to assist training of chemists in molecular imaging.
- Encourage the SNM to play a key role in implementing training programs by providing continuing medical education courses on molecular imaging to residents, fellows, and other practitioners and by providing a forum through which faculty at academic institutions can design and share standardized curricula.
- Encourage the SNM and industrial partners to set up a clearinghouse-type mechanism to assist in moving promising discoveries along in the approval process. By partnering with academia and industry earlier in the process, SNM could help accelerate development. Such a clearinghouse could collect a portion of the royalties and thereby become self-sustaining.
- Encourage academia, with assistance from industry and others, to pursue the approval process to take agents to the clinic.
- Identify ways to support and devise more sophisticated methodologies for assessing the effects of targeted radiotherapies. These should include consideration of biological bystander effect and heterogeneity, as well as the identification of serum biomarkers that reflect the effects of radiation on both tumors and normal tissues.
- Encourage the molecular imaging community to devote effort and resources to the development of radiofrequency contrast agents and create mechanisms by which the community is apprised of the latest developments and possible beneficial applications of these agents.
- Encourage partnerships between molecular imaging researchers and practitioners and research teams who

are working to identify disease biomarkers that may detect early disease. Patients with elevated early-stage biomarkers can then be referred for molecular imaging. Joint meetings and proposals between molecular imaging specialists and pathologists could be one starting point for such collaborations.

- Encourage more hypothesis-driven science in the development and validation of surrogate markers. Develop and carry out such studies to support confidence in the surrogate marker before it transitions to clinical use.

Summary Statement

Basic research supporting molecular imaging development is flourishing as the potential benefits of these techniques in patients with a range of disease and health issues becomes apparent. The immediate challenges are to attract and train new talent from a range of scientific disciplines to bring a synergetic focus on the most crucial questions; to work collaboratively with industry, professional organizations, academia, and regulatory bodies to streamline the bench-to-bedside process, and to identify the right questions that will direct research and discovery in this rapidly expanding field.

Michael J. Welch, PhD
Chair, Basic Research Issues Session

Mathew L. Thakur, PhD
Cochair, Basic Research Issues Session

PRESENTATIONS

Oncogene Cell Differentiation/Cell Transduction

Imaging, in combination with physical examination and pathologic evaluation, is a key element of cancer diagnosis and staging. To date, cancer imaging largely focuses on determining the precise localization of the primary tumor and sites of metastatic disease. Elements of a diagnostic report include the site and size of a cancer as well as the nodal status and the presence of disease in other organs. These end points have improved information available to oncologists and refined treatment regimens. Morphologic assessments of disease, however, provide limited insight into the unique, individual qualities of a particular patient's disease, the knowledge of which could dramatically alter patient treatment and response. This limitation is the driving force behind the development of molecular or personalized medicine. From the perspective of molecular imaging and pathologic diagnosis, the transition from primarily a morphologic assessment into a detailed, real-time molecular diagnosis for each patient would represent a quantum leap in patient care. This would enable molecular description of disease at an early stage, before it is detectable by a physical exam and when it would be more easily treated (*1*).

Molecular events underlie the development of the tissue changes detected in morphologic imaging studies, just as they underlie the histologic changes noted in biopsy specimens. The challenge for diagnostic disciplines is the development of technologies that deliver molecular descriptions of disease to the oncologist. Years of cancer research have uncovered numerous molecules that contribute to an environment conducive to cancer growth and metastasis. A variety of molecules drives the behaviors that are needed for a cancer to form, invade surrounding stroma, and metastasize. To survive a metastatic journey, cells from a primary tumor must detach, migrate within surrounding stroma, cross endothelial cell barriers, survive the intravascular environment, extravasate, continue to migrate, invade the new stroma, form micrometastases, and further proliferate (*2*).

From the perspective of personalized medicine, the molecules that enable this metastatic process to unfold are simultaneously the biomarkers of the disease process and the targets of therapy. Many examples of cancer-relevant molecular interactions have been identified, including those involved in cell–matrix interactions, receptor–growth factor interactions, avoidance of apoptosis, cell motility and associated chemotactic factors, and intracellular signaling pathways that stimulate cell proliferation.

Basic and Translational Research

Immortalized cell lines, primary cultured cells, animal studies, and immunohistochemical studies of patient tissues have provided a rich portrait of cancer pathogenesis. Detailed information has been accumulated at the bench regarding mechanisms whereby a cancer cell senses its environment and thrives within it. A pivotal next step is to determine whether these molecules can be used as in vivo biomarkers of disease.

Direct Study of Human Tissue is Essential

Translational research is focused on understanding how insights gained in the laboratory can be applied to patient disease for diagnostic and therapeutic applications. The role that cell adhesion molecules, such as the integrins, play in mediating intracellular signals highlights the importance