Session 1: Drug Discovery

Participants in this panel addressed key issues relevant to drug discovery, including the application of molecular imaging methodologies to the identification of promising agents and, perhaps more important, to the identification of those agents that may have no clinical relevance.

Steven Bodovitz, PhD, began by outlining trends in innovation in drug discovery. He pointed out that "drug target discovery [has given] way in recent years to the lower standard of biomarker discovery." He went on to address issues associated with biomarker approaches and suggested that if "researchers [are] able to examine . . . how drugs perturb homeostasis, . . . the excitement . . . that surrounded genomics might look tame in comparison."

Biomarkers, however, are not yet routinely applicable to most disease systems, which tend to be heterogeneous. In addition, variability in biomarker expression between patients and perhaps at different times within the same patient is not yet well understood. Bodovitz proposed several questions for discussion.

Next, Richard Pestell, MD, PhD, discussed tissue-specific light-activated gene expression and the current development of animal (particularly transgenic mouse) models that enable the study of inducible gene transfer and expression. The advantages (particularly inducibility and resolution) as well as the disadvantages (lack of depth of penetration of most light activation systems and the current shortcomings of transient protein expression subsequent to photoactivation) of light-activated systems were reviewed.

Several questions emerged:

(1) Can this system for temporal and spatial control of gene expression be applied to human therapies?
(2) Can this system be adapted for temporal and spatial control of multiple genes?
(3) What are the challenges (biologic and regulatory) associated with clinical use of gene activation approaches?
(4) What are the general technical issues facing photoactivation?

Eric D. Agdeppa, PhD, next addressed the design of peptide imaging probes. After briefly describing macromolecules in development, he focused on peptides for imaging, with attention to sensitivity and other criteria for the various imaging modalities. His discussion touched upon the myriad questions that are key to the understanding and development of peptide molecules.

Chaitanya Divgi, MD, then discussed therapeutic antibodies. After reviewing the state of the art of radioimmunotherapy (RIT), he presented preliminary clinical data on the use of antibody PET to optimize immunotherapy development and trial conduct. Again, many significant questions were identified, particularly:

(1) Why is lymphoma RIT not as widely utilized as it should be?
(2) What are the social and professional barriers to optimal use of RIT?
(3) What are the key considerations that should guide the use of radiolabeled antibodies to optimize immunotherapy?
(4) What are the regulatory issues surrounding use of radiolabeled macromolecules in the clinical context?

The session concluded with an overview by Juri Gelovani, MD, PhD, of the use of molecular imaging to "facilitate the development and clinical translation of novel tumor-targeted molecular therapies." The presentation described the use of molecular imaging for pharmacokinetic and pharmacodynamic studies, as well as "non-invasive molecular imaging of spatial heterogeneity of target . . .[to] facilitate image-guided therapeutic intervention." The use of imaging approaches to develop molecular profiles of individual cancers was also discussed. Among the questions raised were:

(1) Who are the most likely researchers to bridge the translational gap from molecular science to clinical practice? Do we need to assemble teams? Do we need to train physicians in molecular science and/or molecular scientists in medicine?
(2) Drug companies have been slow to embrace the use of biomarkers in clinical trials, despite their potential. One reason appears to be systemic: the current goal is to move drug candidates through clinical trials as quickly as possible, not necessarily to increase data collection. How can we improve this process?
(3) What is a biologically effective dose, and what are the factors that determine the dose for diagnostic and therapeutic agents?
(4) What are the trade-offs with targeting agents? If they are used to determine/optimize biologically effective (not maximum tolerated) doses, what are the cost and safety issues and other potential problems?

This session and the follow-up discussion and consensus-seeking session encouraged greater mutual understanding between researchers and clinicians on the current state of molecular imaging in drug design, discovery, and development. In addition to providing an overview of the roles nuclear and molecular medicine can play in drug development, the sessions offered a solid base of key concerns and goals for attendees as they rise to the many challenges ahead.

Discussion: Trends and Challenges

Discussion among summit participants in the Drug Discovery breakout session focused on identifying challenges and promising strategies for meeting these challenges in the current environment of rapid technological change. Participants agreed that molecular imaging in drug *discovery* is fairly well established in large companies and that most smaller companies are at least aware of the potential. However, several participants noted an urgent need to provide both industry and federal regulatory and funding bodies with additional education, information, and updating on the importance of molecular imaging in all stages of drug *development.*

One key challenge that emerged was in identifying ways to increase willingness by both the pharmaceutical industry and the U.S. Food and Drug Administration (FDA) to build nuclear imaging into earlier stages of the drug development process, including preclinical studies. The optimal strategy suggested by the group would first involve the pharmaceutical industry building a "comfort level" based on clinical and then preclinical successes with molecular imaging. Industry would then partner with molecular imaging professionals in demonstrating these successes to the FDA and other rule-making bodies.

The importance of an active and engaged role for the SNM in improving the status of molecular imaging in drug discovery and development was a key conclusion by the discussion group. The society brings a reputation for integrity and unbiased scientific knowledge to high-level interactions with industry and regulatory bodies and is in a unique position to provide convincing evidence of the value of molecular imaging, particularly in pharmaceuticals targeted at oncology, cardiology, and neurology applications.

Recommendations

Recommendations for action were made in several broad areas by participants in the discussion group. Although the SNM could not be expected to take immediate or comprehensive action in all of these areas, the society is well placed to take a lead in partnering with other groups in these efforts. The summit group recommended action to:

- Focus on strategies that will provide convincing evidence for FDA acceptance of specific imaging biomarkers for disease states. Among the specific strategies outlined for these efforts were:
  - Increasing efforts to validate imaging biomarkers and surrogates through pathology, outcomes measures (both response- and survival-based), and standards for reproducibility. Standards for reproducibility could include comparison of findings in different conditions and on different equipment, establishing investigation parameters (including animal models, clinical characteristics, etc.), and proven methods for quantification of test results.
  - Encourage research and development of next-generation imaging biomarkers, particularly in diseases not yet explored with imaging biomarkers and in investigation of downstream biomarkers.
- Increase both industry and regulatory awareness of the different roles that radiopharmaceuticals can play in both drug discovery and development. Roles for radiotracers include early screening studies, pharmacokinetic and pharmacodynamic studies; safety and targeting investigations; and utility in assessing efficacy and in prediction of response. The potential for a dual role for radiopharmaceuticals in both therapy and diagnostics in some studies should be emphasized as well.
- Work to establish credible and well-recognized groups that can identify issues and provide guidelines for the use of molecular imaging in drug development and discovery. Such an effort will be especially important in the validation of specific biomarkers. Effective groups include members of the SNM, the larger molecular imaging community, industry, and federal bodies such as the National Institute of Standards and Technology, the National Institutes of Health and/or its affiliate institutions including the National Cancer Institute, and the FDA.
- Develop and nurture networks of influence with imaging constituencies outside of nuclear medicine (including communities focusing on MR imaging, optical imaging, etc.).
- Develop, update, index, and make easily accessible a library of supporting literature on the significance of molecular imaging in drug discovery.
- Identify ways to encourage and nurture the development of well-informed and well-trained regulatory experts, radiochemists, imaging modelers, and health technology assessment experts who can work closely with molecular imaging to advance acceptance and application across a broad range of preclinical and clinical studies.
- Consider ways to facilitate dialog and cooperative interaction with the FDA. One suggestion was to work with the FDA in creating SNM-approved or -accredited imaging centers.
- Work with clinical trials groups to decrease barriers to inclusion of molecular imaging, which is sometimes perceived as too costly or cumbersome.
- Provide consensus expert advice for academic centers and corporate research organizations on the Good Laboratory

Practice (GLP), Good Clinical Practice (GCP), and Good Manufacturing Practice (GMP) functions needed to validate studies and maintain quality standards.
- Continue to work to increase the positive image of molecular imaging and to counter negative impressions, particularly those associated with difficulty or danger in pursuing the development of novel tracers from discovery through approval and clinical application.

Summary Statement

Molecular imaging already plays an important role in drug discovery and development, and this role is likely to increase greatly within the next decade and into the foreseeable future. The most urgent action needed to facilitate and accelerate this trend is to create an effective and collaborative effort among molecular imaging practitioners, scientists, industry, and government to work together to establish research databases, construct libraries of validated surrogates and image data, devise and promulgate standards and guidelines, and define the good practices and quality assurance measures that can support reliable research. The SNM is ideally situated to take the lead in forming such a collaborative effort.

Chaitanya Divgi, MD
Chair, Drug Discovery Session

Alexander McEwan, MD
Cochair, Drug Discovery Session

PRESENTATIONS

Trends in Innovation in Drug Discovery

Back in the heyday of the genomics era, it was common to hear predictions about how easily drug targets could be found. Simply by looking at the differences between normal and diseased genomes, the targets for therapeutic intervention would fall out. The premise was that at least some of those differences must have causal relationships with diseases. Although this is true to some degree, the background noise was surprisingly high. The systems under investigation are enormously complex, and differences are more often than not the result of normal variations rather than the causative elements of diseases. The sobering reality crashed the genomics hype but laid the foundation for new approaches for drug discovery that account for the enormous complexity in biological systems. The success of these approaches, however, will likely depend on methods to reduce complexity. Gene and protein expression will always be complex, but phenotypes need not be. New imaging technologies hold enormous promise for accurate identification and characterization of disease phenotypes.

Millennium Pharmaceuticals epitomized the genomics-based target discovery hype in the late 1990s. The company signed more than $1 billion worth of partnerships and alliances for drug targets, including a blockbuster deal with Bayer at the end of 1998 for 225 targets over 5 years at a total value of $465 million. But none of these targets yielded approved drugs. In fact, Millennium has since changed its business model and minimized genomics research.

The challenge is that even a single cell is a complex system. A recent study by Jonathan Weissman's group at the University of California–San Francisco characterized the noise in *S. cerevisiae* at both the gene and protein expression levels in single cells (*1*). The researchers reported that the noise in protein levels (coefficient of variation ≅30% for low- to medium-abundant proteins) most likely originates from the stochastic production and destruction of low-abundance mRNA molecules (1–2 cell). The researchers also reported that variation in protein levels is highest for proteins that respond to the environment and lowest for those involved in housekeeping operations, such as protein synthesis, which means that the most interesting proteins in terms of drug development are likely to be the noisiest. The complexity increases when cells form tissues and bodies. Sources of variability at these higher levels include: diet, exercise, rest, stress, work, medications, illnesses, etc. (*2*). Controlling for all of these variables is critical for reducing noise but is practically impossible.

Given all of this complexity, it is not surprising that drug target discovery gave way in recent years to the lower standard of biomarker discovery. Although a target needs to have a causal relationship to a disease, a biomarker does not. No longer do drug developers expect to have a treasure trove of new targets. Instead, they hope that the biomarkers can play an important supporting role in improving the efficiency of clinical trials by: (a) earlier identification of efficacy and/or toxicity and (b) stratification of patients into good and poor responders.

Given the complexity, identifying single biomarkers with significant prognostic power may be difficult, but combining them has the potential to improve performance. The concept is straightforward: the more partially predictive or partially