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.

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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

diagnostic elements that are combined, the greater the overall accuracy. The reality, of course, is not quite so simple, because each biomarker has inherent variability among individuals. One person might have a higher level of a particular biomarker with no disease or vice versa (*2*). If finding a cut-off value between normal and disease can be difficult for a single biomarker (as a result of genetic variation between individuals), the process becomes even more difficult in the case of patterns (*2*). On the positive side, however, biomarkers are not completely fraught with noise. The level of a given protein can correlate well with a specific disease in an individual, and the level of a given protein has been shown to be very stable in an individual over time (*2*).

Despite the challenges, the value of patterns is beginning to live up to its potential. Patrick Brown at Stanford University, for example, has used DNA microarrays to classify breast, gastric, and pancreatic tumors. Moreover, several companies, such as CuraGen, Gene Logic, Iconix Pharmaceuticals, and PHASE-1 Molecular Toxicology, have used DNA microarrays to generate profiles of efficacy, toxicity, and mechanisms of action of potential drugs, although the utility to drug developers remains an open question (*3*). On the proteomics side, progress has been in fits and starts, but recent examples of promising results include the work of Stephen Kingsmore, from the National Center for Genome Resources, in identifying patterns of blood proteins that predict the progression of sepsis, and the work of Lance Liotta and Emanuel Petricoin, III, from George Mason University, in identifying patterns of blood proteins that diagnose the earliest stages of ovarian cancer. More research must be done (*4,5*).

Although these biomarker approaches are addressing the challenges of biological complexity, they do nothing to reduce complexity. Given the mixed results thus far, a new emphasis on reducing complexity would be a welcome advance. Gene and protein expression appear to be able to occupy a wide range of states, but cells, tissues, and bodies cannot. The individual molecular states integrate to a much smaller set of phenotypes. This is the fundamental principle of homeostasis. More detailed knowledge of these homeostatic phenotypes holds enormous promise for biomarker research. At the present time, diseases are defined in relatively gross terms, but if phenotypes could be reduced to a specific set of homeostatic states, then much of the molecular noise could become signal. Rather than comparing multiple molecular homeostatic signatures with multiple phenotypes, a one-to-one correspondence would be possible. The result would be a significant and possibly critical reduction in complexity.

Elucidating these homeostatic phenotypes is clearly a significant challenge, especially in terms of disease states in vivo, but advanced imaging technologies may be up to the task. Ideally, researchers would be able to distinguish between all of the possible disease phenotypes, from subtype to stage to growth rate to comorbidities. In addition, researchers would be able to examine, in something close to real time, how drugs perturb homeostasis. With such capabilities to reduce complexity, the excitement of yesteryear that surrounded genomics might look tame in comparison.

Among the key sets of questions to be addressed in reaching such a goal are:

(1) How heterogeneous are most diseases? How many can be accurately subtyped? Of these, how many have yet to be subtyped? Of the total subtypes, how many can be (or are likely to be) characterized by morphologic changes versus molecular changes?
(2) Should a greater emphasis be placed on longitudinal studies for biomarker discovery and validation? If interpersonal variability is high, does it make sense to examine intrapersonal variability? If so, what is the best approach? Should we start collecting blood samples from tens of thousands of people? How would we control for variables such as diet and exercise? Who would pay for the biobank?
(3) Many biomarker discovery programs are based on de novo research but have yet to yield large numbers of successes. By contrast, drug developers already know the target(s) of their drug(s) and appear to be having a great deal of success using these and related molecules as biomarkers for evaluating drug activity in clinical trials. Should biomarker research minimize the first approach and maximize the second? Is the focus of the second approach a good way to reduce variability and complexity? In addition, the second approach is based on perturbations. Do perturbations increase signal to noise, especially against a background of high variability and complexity? If so, are there ways to incorporate perturbations in biomarker research even when drugs are not safe or available?
(4) What is the value to physicians of a nonspecific biomarker that indicates only that something is wrong but not necessarily what is wrong? C-reactive protein would be a good example. Is it helpful to physicians (or does it make their lives miserable) to require extensive follow-up testing? What is the value of a nonspecific biomarker to payers? Will they reimburse for it and for follow-up tests?

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