Industry Watch

Medical Imaging in Drug Discovery — Part II

Molecular imaging is beginning to be applied to pre-clinical drug development efforts, and a number of new companies are poised to serve this market, touting their molecular imaging technologies as specifically aiding drug development.

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In our last column (*PharmaGenomics* **4[1],** 16–19 [2004]), we began to explore the shift to a broader-than-diagnostic view of the value of imaging technologies. It stands to reason that imaging should play some broader role. After all, as Robert Dunkle reports in a recent article, "Up to 70% of the experiments in pharmaceutical research and development result in an image as an output" (1).

Of course, Dunkle is referring to virtually every kind of image one could imagine, from a snapshot taken of a slide through a microscope to the kinds of magnetic resonance images (MRIs), computed tomography (CT) scans, positron emission tomography (PET) scans, X-rays and ultrasounds we discussed last month. But even considering only "high-tech" imaging, its use in discovery and development definitely is on the rise.

In this column, we want to explore issues related to imaging at the molecular level. Molecular imaging merges the modern tools of molecular and cell biology with state-of-the-art technology. The goal is to develop technologies and assays for imaging molecular and cellular events in living organisms, thus aiding in finding better methods for studying biological processes. It's truly interdisciplinary: "The term 'molecular imaging' implies the convergence of multiple image-capture techniques, basic cell/molecular biology, chemistry, medicine, pharmacology, medical physics, biomathematics and bioinformatics into a new imaging paradigm" (2).

We're interested in what molecular imaging can do for drug development and discovery. Can it improve the drug development process? In what specific activities could it be most useful? One note: we're indebted to David Wine, a graduate student at the MIT Sloan School of Management, who produced an outstanding overview of the issues in a literature review he prepared for a class — Research Themes in Management of Technology (3).

A New Discipline

The first thing to say about molecular imaging is that it is relatively new. As a scientific discipline, it dates back roughly to 1993, although it is growing in scope and influence. Medline and PubMed only recently added "molecular imaging" as a subject term. Three dedicated journals have emerged in the past three years, and there are three specialized annual scientific congresses now devoted to the discipline. The Society for Molecular Imaging (SMI, Stanford, California, USA) was founded in 2000 as an "international scientific educational organization whose purpose is to advance our understanding of biology and medicine through noninvasive *in vivo* investigation of cellular molecular events involved in normal and pathologic processes" (4).

Accelerating pre-clinical drug development is one of the key areas of focus for scientists involved in molecular imaging. It is one of three "overarching areas" in which molecular imaging has advanced dramatically of late, and was one of the main topics at the SMI's annual meeting in San Francisco, California, in August 2003. As the society's press release for the meeting explains:

"Problems in pre-clinical drug development have been addressed through advances in [molecular imaging]. First, typical assays for drug efficacy have required the excision of tissue, biopsy or necropsy, and these assays are slow and subject to sampling errors. Relatively inexpensive tools have been invented to produce rapid whole-body analyses, which provide better information more rapidly, thus enabling more sophisticated drug studies in animals. These advanced approaches, currently used in animal studies, will improve the design of clinical studies and ultimately make better drugs available

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sooner. Second, understanding the mechanisms of action for drugs at the molecular level is key to effective development of novel therapeutic strategies. [Molecular imaging] enables analysis of the target as well as the delivery of the therapy" (5).

Molecular imaging involves several technologies, including single photon emission computed tomography (SPECT), PET, MRI, CT and ultrasound. According to the Society of Noninvasive Imaging in Drug Development (SNIDD), which is an institute of the Academy of Molecular Imaging (Los Angeles, California, USA), these "noninvasive imaging techniques can be used to obtain information on *in vivo* biochemistry and physiology in experimental animals and man that cannot be obtained in any other way. As applied to drug discovery and development, information obtainable via imaging can be divided into four categories: 1) determination of desirable, pharmacological effects or undesirable side effects (i.e., the effect of the drug candidate on *in vivo* biochemistry and physiology); 2) the interaction of a drug or drug candidate with the desired target (e.g., receptor, enzyme or transport system), including dose occupancy relationships and kinetic information; 3) the delivery of a drug to a specific target and 4) the absorption, distribution, metabolism and elimination of the labeled drug candidate" (6).

What About Drug Development?

One of the keys to molecular imaging's value in drug development is probes, which provide the imaging signal or image contrast in most molecular imaging assays. They are similar to stains used in histological analysis of tissue samples, but unlike stains, they are injected into living subjects to create images of specific biological or molecular events. Many probes are discovered by chance, but "recent advances in the drug discovery process will aid in future selection and/or rational design of newer probes through combinatorial chemistry and high-throughput testing. It is anticipated that increasing multidisciplinary interactions between imaging research groups and the pharmaceutical industry will have a significant impact on the design and development of many more novel molecular imaging probes. This is because drug development shares many features in common with molecular imaging probe development, and the two fields likely will continue to influence each other" (2).

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The economic and scientific hurdles are high, though, as those in the pharmaceutical industry who use molecular imaging are finding out. Cancer therapies offer a case in point, as two physicians from the National Cancer Institute (Bethesda, Maryland, USA) pointed out in 2000:

"Although substantial improvements in imaging technology constantly are being made and new imaging devices are on the horizon, imaging's greatest opportunity to play a pivotal role in the post-genomic era may be through the development and implementation of highly specific molecular imaging probes. However, this ability to elucidate an array of targets and generate specific therapies and probes creates a practical dilemma" (7).

Referring to the high level of risk from the continually increasing cost of drug development and clinical introduction and the decreasing productivity of pharmaceutical R&D, they continue: "With this level of risk, commercial pharmaceutical companies must carefully evaluate the market potential, realizing that only candidates with broad application in both market share and sales volume are likely to represent a rational business decision…Many therapies designed to interact with specific molecular targets are likely to have limited market potential…Imaging probes to elucidate and interrogate these targets may be even more vulnerable than their therapeutic counterparts. However, the development of clinical imaging probes that will enable a better understanding of cancer *in vivo* at the molecular level represents an extraordinary opportunity. The greatest challenge to realizing this opportunity, however, is the seemingly endless number of targets and possible probes" (7).

A Growing Industry

The opportunity, no matter how daunting, is attracting a lot of industrial players. On its links page, the Molecular Imaging Central web site (www.micentral.org) lists more than 50 companies and research institutes involved with molecular imaging (8). The large pharmaceutical companies, anxious about declining drug development efficiency and looking for ways to make improvements, are supporting many efforts to supply research markers to help evaluate lead compounds early in development. And many smaller companies are touting their technology developments in molecular imaging as specifically aiding drug development.

For instance, in May 2003, Advanced Research Technologies Inc. (ART; Saint-Laurent, Quebec, Canada) announced the development of a proprietary molecular imaging technology "designed to characterize and measure cellular and molecular processes and pathways." Citing the significant portion of drug development costs associated with pre-clinical trials involving toxicity and efficacy testing on animals, ART suggested that its new technology could "help reduce critical labor and testing costs while providing vital information…identify[ing] unintended drug targets, thus adding important information about drug pathways and potentially saving millions of dollars in development costs." The company's R&D vice president claims that the new system also will "improve markedly the time-to-market of new drugs" (9).

Dunkle describes another company, Xenogen (Alameda, California, USA), as offering "an integrated suite of imaging and transgenic technologies that typify

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how many new methods utilize imaging to advance drug discovery. *In vivo* biphotonic imaging illuminates biological processes taking place in a living mammal, providing a "window" into the organism, and makes possible the tracking of biological activity in real time, at the molecular level" (1).

At Genentech (South San Francisco, California, USA), the Biomedical Imaging Group is using *in vivo* imaging techniques in late-stage immunology, oncology and vascular biology research projects. As Nicholas Bruggen, a Genentech senior scientist, writes: "The majority of our research efforts are focused on gaining an understanding of *in vivo* physiology and drug action from knowledge of the biophysics of the biological process. For example, we are developing ways to assess tissue perfusion and blood vessel morphology in order to evaluate the potential for VEGF and other growth factors as part of our therapeutic angiogenesis initiative. This is achieved using a number of approaches, including functional MRI imaging techniques, to measure skeletal muscle metabolism and blood flow, as well as angiographic techniques to demonstrate large vessel blood velocity."

Molecular Imaging Research Inc. (Ann Arbor, Michigan, USA) has brought the contract research organization model to molecular imaging. The company provides pharmaceutical and biotech companies with pre-clinical evaluation of novel anti-cancer agents, conducting contract research for preclinical evaluation of novel anti-tumor agents using xenograft, orthotopic and transgenic animal models.

These are but a few examples of companies beginning to operate in the imaging technologies for drug discovery marketplace.

A Mission-critical Component of Discovery and Development

In his article, Dunkle poses a question: can drug discovery and development be accelerated using image informatics? "Absolutely…," he writes. "Acceleration occurs through productivity improvements, better experiment interpretation and new insights derived within a single lab. When applied across labs ranging from target identification through to clinical [testing], acceleration across the entire process multiplies…it is a mission-critical component of drug discovery and development" (1).

David Wine makes a strong case for the value of this technology to the drug development process. Having illustrated all the places along the drug development pipeline that could benefit from molecular imaging, he returns to the focus of his paper: the use of the technology with small animals. It's a good bridge to the third part of our column series on imaging, where we will explore the "whole body" approach.

Probes are one of the keys to molecular imaging's value in drug development; they are injected into living subjects to create images of specific biological/ molecular events.

"Molecular imaging of humans in clinical trials has the promise to significantly reduce the time needed to establish whether a treatment is effective and to reduce the size of the trial," writes Wine. "Why, then, is this study focused on molecular imaging in small animals? One reason … is that it is far easier to satisfy the requirement to demonstrate efficacy of the chosen methods. Since the stakes are high, the development organization should be confident the methods work and are relevant. However, it is orders of magnitude faster and cheaper to establish this confidence than to seek FDA approval of a new diagnostic or therapeutic agent meant to be injected into people" (3).

The direct improvements to the development pipeline Wine posits are nothing to scoff at. The crisis of R&D productivity faced by big pharma has enormous financial implications. The ability to make an earlier decision about whether to pursue or discontinue development of a drug candidate could go a long way to improving the picture. Speedier progression to clinical trials means faster time to market. These are serious benefits.

FDA rightly contends that "the industry needs new research and tools that will lead to more efficient and successful development and testing of drugs" and "better ways to evaluate safety and to figure out at an early stage if the product is working" (10). Molecular imaging is one of those tools, with considerable promise. Our next column will explore the use of molecular imaging in small animals — and even in humans — not as a diagnostic tool but as a technology to advance the drug development process.

References

1. R. Dunkle, *Drug Discovery World*, **Winter,** 75–82 (2003–2004).
2. T.F. Massoud and S.S. Gambhir, *Genes Dev.* **17(5),** 545–80 (2003).
3. D. Wine, *Molecular imaging in drug development – A literature review.* MIT Sloan School of Management, Fall 2003.
4. The Society for Molecular Imaging, Accessed at www.molecularimaging.org/mission.php3.
5. The Society for Molecular Imaging. *Society for Molecular Imaging's second annual meeting highlights diversity and speed of molecular imaging advances.* Press release, August 15, 2003.
6. Accessed at www.snidd.org.
7. J.L. Tatum and J.M. Hoffman, *Acad. Radiol.* **7,** 1007–1008 (2000).
8. Accessed at www.mi-central.org/links/industry.html.
9. ART Advanced Research Technologies Inc. *ART announces innovative molecular imaging technology.* Press release, May 23, 2002. Accessed at www.art.ca/en/press/2002_05_23.html.
10. A.W. Mathews and S. Hensley, "FDA explores obstacles to new drugs: Agency calls for new research and tools – and thinks it can help." *The Wall Street Journal Online*, **March 16,** 2004.**PG**