a focus on MOLECULAR IMAGING

By combining cutting-edge biomedical research with the time-proven ability to visualise the unseen, the rapidly emerging field of molecular imaging promises to open new vistas for a wide range of individuals, from basic researchers to scientists working in drug discovery and development and to physicians in medical practice.

By Dr Ken Rubenstein

Molecular imaging is undergoing rapid research advancement and commercial development, driven largely by big pharma's burgeoning interest in biomarkers as crucial for decision support in preclinical and early clinical development.

In vitro biomarkers have been used for decades, but the introduction of postgenomic research tools for studying gene, protein and metabolite expression opened exciting new opportunities to explore various aspects relating to mechanism, safety, and efficacy. *In vivo* imaging biomarkers complement and augment *in vitro* and *ex vivo* types by pointing to the location in the body of diseased tissue and monitoring the effects of therapeutic agents. Molecular imaging takes these abilities a step further by moving beyond morphology into a world where dwell the molecules affected by disease and the therapies used to treat it.

Advances in molecular imaging are limited by the availability of new and diverse imaging agents for use in humans. These *in vivo* agents are, in effect, drugs, and therefore fall under similar regulatory controls. Although the stringency of these regulations has been relaxed to a degree, given the small quantities of agents introduced, the expense and time involved in developing them still limits their supply. More such agents have emerged in recent years and their numbers continue to grow steadily. The promise is great, and the troika of academia, large companies, and small companies is currently shaping an ecological system that promises to accelerate advances in the field.

Technologies: a rich history

In vivo imaging dates back to 1895 when Roentgen discovered the medical utility of x-rays. Within five years chest x-ray images were used to diagnose tuberculosis. In the next decade contrast media enabled imaging of the kidneys and GI tract. The x-ray imaging field continued to advance with new applications emerging through the first half of the 20th century. Ultrasound came into the picture around 1960, enabling a major advance in real-time imaging of organs and fetuses in motion. By 1970 mammography entered the picture and began saving lives of women with early breast cancer.

Shortly thereafter, computed tomography (CT) opened the fertile field of digital radiography, which not only increased resolution of images, but

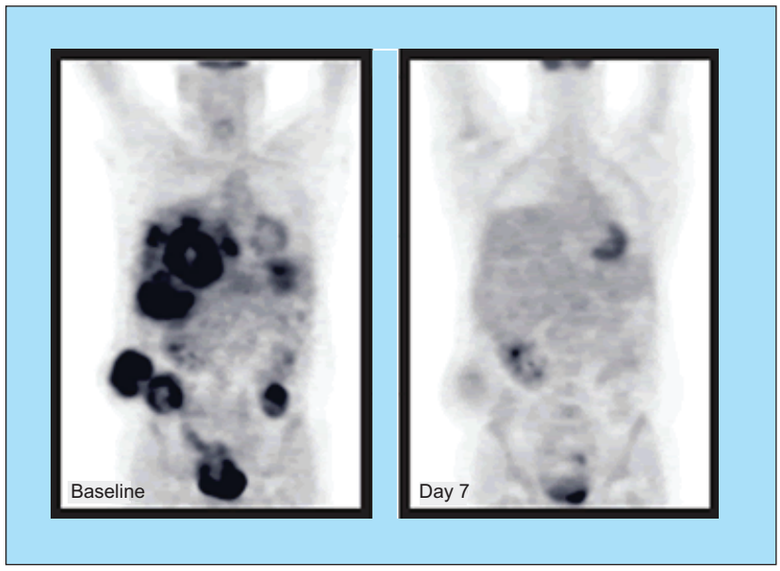

Figure 1
FDG-PET tumour scans taken before treatment and seven days after the start of treatment
Source: Branca MA. Proof of concept: pharma's new watchwords. PharmaDD. May/June 2006. www.pharmadd.com/archives/May_16_2006/POC%20Pharmas%20New%20Watchwords.asp. Accessed June 15, 2007

provided new means for storing and sharing data. Magnetic resonance imaging (MRI) came on the scene in the 1980s, providing another leap forward in diversity of applications and image sharpness. Morphological applications of MRI were soon extended to functional imaging. Even more important from our perspective, the mid-1980s saw the introduction of clinical positron emission tomography (PET) and the start of molecular imaging.

PET, the most prevalent molecular imaging technology for biomarker work today, involves injecting a compound containing a positron-emitting radioisotope (often F18 or C11) into the body, allowing it to reach its target, and detecting its location and quantity with a PET scanner. Since the isotopes have half-lives of two hours or less, instruments must be used in proximity to a cyclotron for their production and to chemical facilities for their conversion into the agent. A scanner and cyclotron require capital investment exceeding one million dollars.

PET's resolution down to the millimeter level permits application not only to humans for diagnosis and drug development, but also to animals for preclinical studies. PET's ability to translate studies from animals to humans adds to its appeal. Sensitivity is also high; isotopes can be detected down to the 100 picomolar level in target tissues. At these low levels the compounds often have little or no physiological effect on the patient or test animal, which permits studying mechanism of action or biodistribution independent of any physiological consequences.

Single photon emission CT (SPECT) is similar to PET in its use of radioisotope-labelled compounds as imaging agents, but in this instance the isotopes are low energy gamma ray emitters such as In111, Tc99m, and I131. SPECT images, which are recorded using gamma cameras that can be rotated around the subject to produce tomographic images, are about one order of magnitude less sensitive than PET images. Although decreased resolution has militated against using SPECT in comparison to PET imaging, the former is making somewhat of a comeback.

Magnetic resonance imaging (MRI) in its many modalities and ultrasound are both contributing greatly to the *in vivo* imaging biomarker revolution, but their applications tend toward the morphological and functional end of the application spectrum. MRI has potential for molecular imaging, but has not yet made a significant impact in practice.

Optical imaging, on the other hand, is making substantial contributions to molecular imaging by virtue of its ability to detect fluorescent and luminescent molecular probes inserted into the body. The introduction of new instrument technologies, especially those incorporating cooled CCD cameras, has enabled the extension of optical imaging to detection of labelled molecules *in vivo* in small animals. Studies based on such optical technologies are becoming increasingly popular in preclinical drug development. Fluorescent and bioluminescent reporter gene assays, which reveal whether particular genes are expressed, have been particularly useful in this regard. Unfortunately, the depth of imaging is limited to only a few centimeters beneath the body's surface, which limits utility in humans or large animals. Signals are reduced roughly an order of magnitude per centimeter depth.

Imaging biomarkers in drug development

Biomarkers are becoming increasingly important for both pharmaceutical and biotechnology companies, especially as supportive elements for deciding whether drug candidates should be advanced, shelved or abandoned. Whereas molecular biomarkers measured *in vitro* provide information on biological pathways that are active in organisms under various conditions, *in vivo* imaging biomarkers add spatial and temporal character to investigations of drug mechanisms, disposition and efficacy.

However, relatively few molecular imaging probes have yet been approved for use in humans. In the United States, exploratory Investigational New Drug applications (INDs) have expanded

pharma's ability to employ molecular imaging agents without full-bore safety and efficacy demonstration, but barriers of resource allocation still limit their potential in drug development. However, their value in proving mechanisms and concepts is nonetheless contributing to their increased use today. Their ideal clinical application as stand-alone surrogate endpoints for use in efficacy demonstration in late-stage clinical development remains largely an attractive possibility awaiting more aggressive validation efforts.

No such limitations exist in preclinical animal studies. Use is widespread, growing rapidly and promises continued rapid growth for the foreseeable future. MicroPET is the dominant molecular imaging modality used today in clinical studies, but optical imaging is coming on strong, limited to an extent by intellectual property concerns. A disadvantage of optical imaging is that available technologies have limited penetrability into living organisms, which favours small animal work, but complicates the translation to humans.

Molecular imaging in diagnostics

Fluorodeoxyglucose-PET (FDG-PET), which finds widespread use in the development of drugs for oncology and other disease areas, likewise finds broad application in diagnosis, staging, monitoring and prognostication in human diagnostics. Indeed many applications of FDG-PET are reimbursable in the United States, and other agents may follow suit. This bright picture is marred by potential cuts in reimbursement mandated by deficit reduction legislation passed in 2005. Although molecular imaging finds its greatest diagnostic application in the area of oncology, needs are greatest, arguably, in the areas of cardiovascular and neurological/psychiatric diseases.

FDG-PET has been shown valuable in detecting ovarian cancer recurrences, and fluoroestradiol-PET (FES-PET) is valuable in quantifying estrogen receptors in breast tumours for predicting drug response. A testosterone-based PET agent shows early promise as a PET tracer in studying the biology of prostate cancer metastasis. A PET agent bearing a peptide known as RDG shows promise for detecting angiogenesis associated with tumour metastasis. A SPECT agent equivalent to FDG is under development and may open the market to the many institutions that have no PET scanner but do own one of the more ubiquitous gamma cameras.

In cardiovascular medicine, FDG-PET is used to assess viable myocardium and can also play a role in assessing cardiac perfusion. A PET agent specific

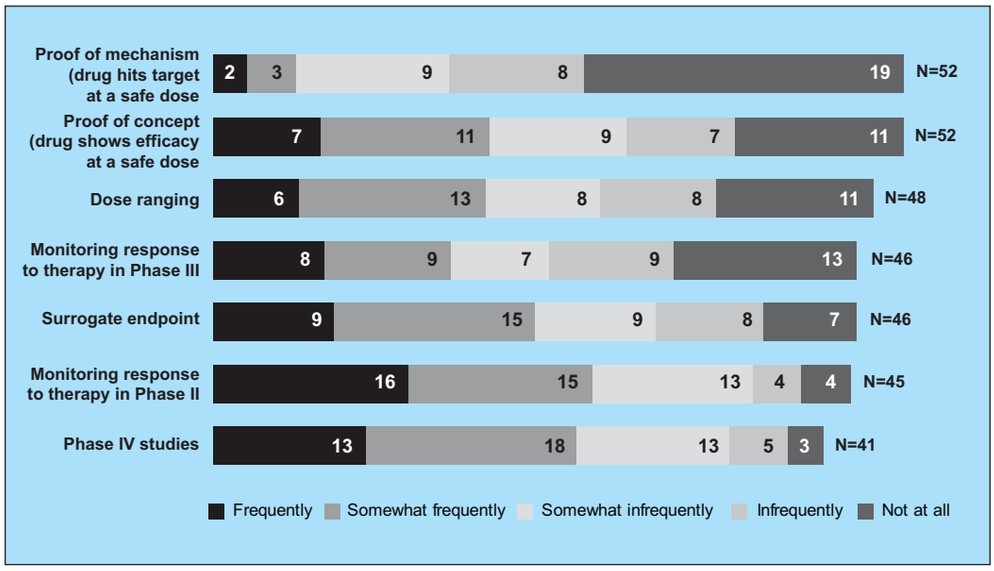

Figure 2
Approaches used for molecular imaging in clinical studies. If your organisation uses molecular imaging in clinical studies, please rate your use of the following approaches. n = 56
Source: Insight Pharma Reports. Molecular Imaging Survey, October 2007

for adrenergic receptors may prove useful in diagnosing heart failure and other cardiac disorders. A SPECT agent, MIBG, has a role to play in identifying patients at risk for potentially fatal dysrhythmias. Another SPECT agent, BMIPP is in development for detection of cardiac ischemia without need for a stress test.

In the neurology area, early diagnosis of Alzheimer's disease is an attractive target, which will become even more attractive if one or more drugs now in development prove more useful than current entries. *In vitro* diagnosis is complicated by the need for invasive collection of cerebrospinal fluid in order to capture molecules from the brain before major dilution in the bloodstream. A number of PET-based molecular imaging agents specific for brain amyloid plaques and tau-based tangles show promise in development for early detection and differential diagnosis of Alzheimer's disease.

Market considerations

The molecular imaging marketplace consists of three main supplier factions: large corporations, small corporations and contract research organisations (CROs). Researchers in the commercial sector provide new instrument and reagent technologies, but academic researchers also have a significant role to play in generating new concepts and testing their feasibility. On the consumption end, pharmaceutical and biotechnology companies use instruments and reagents for preclinical and clinical development directly in-house and indirectly through CROs and academic centres.

The large corporation supplier segment is dominated by three companies, each representing extensive molecular imaging product lines: GE Healthcare, Philips Medical Systems and Siemens Medical Solutions. The smaller company segment consists of a relatively large number of organisations addressing particular market segments; namely radiopharmaceutical products, instruments, software and services.

The molecular imaging field viewed from the market perspective is young, and its ultimate structure and dynamics are still being formed. It is difficult for a large company to maintain healthy growth based on instruments alone, and the big three players accordingly are, to varying degrees, addressing reagent and consumables markets for imaging humans despite regulatory and financial disincentives. These latter limitations make the preclinical market particularly attractive, and companies have been highly proactive in addressing associated marketed opportunities.

Although PET dominates molecular imaging based on sensitivity and quantifiability, SPECT technology has been improving and thereby becoming more competitive. PET applications will continue to dominate the mid-term picture, although SPECT remains a dark horse candidate looking beyond the next five-year period.

With regard to drug discovery and development, molecular imaging will continue to grow rapidly, driven both by PET and optical imaging. Preclinical imaging is growing faster than clinical imaging, driven by pharma's need for ever-earlier attrition of unpromising drug candidates. Phase III and IV clinical trials remain the largest market

opportunity in pharma simply because they deal with many more patients than earlier development phases. However, pharma has not yet shown any great impetus to address development and validation of the surrogate markers needed to replace less objective and timely clinical endpoints for demonstration of efficacy.

In considering business models of major integrated manufacturers in the molecular imaging market, these companies face inherent difficulty in leveraging their instrument placements and benefiting from high-margin reagent sales. The *in vitro* diagnostics industry has faced the same set of issues for decades. It is difficult to devise a closed system, where a proprietary reagent must be used with only one brand of instrument. Manufacturers can spend time and money developing a sophisticated proprietary reagent (risking failure at any point in the development cycle) only to find that their investment (which can be very substantial in the case of molecular imaging in humans) may benefit competitors. Although there are sales strategies for tying reagent sales to a particular manufacturers' instrumentation, there is little companies can do to control the fate of reagents once they leave the factory. So, although healthcare can clearly benefit from new high-margin molecular imaging agents, development cycles are long compared to instrument cycles, and risks abound.

Future market opportunities may be driven either by short-range business considerations or a longer term vision based on the belief that molecular imaging has a key role to play in the emerging field of personalised medicine. Each of the big three players in molecular imaging take both perspectives into account, but some are clearly more driven by the personalised healthcare vision incorporating *in vitro* diagnostics, molecular imaging and information technology.

The molecular imaging ecological system of large companies, small players, and universities has been quite active in deal-making during the past few years. Tabulation and analysis shows that the most prevalent deal category pairs imaging instrument and agent suppliers with pharmaceutical companies. Lower levels of activity were observed for deals between suppliers and universities, and those involving acquisitions. PET and SPECT technologies were represented most frequently in deals considered. Optical imaging followed close behind in frequency.

Market size and growth prospects

Molecular imaging instrument revenues are projected to nearly double the 2007 total during the subsequent five years. Reagent revenues are expected to grow even faster during that period, by just over two-fold. PET placements represent a large majority of both current and projected revenues for both instruments and reagents. Optical imaging is expected to experience the fastest growth among the three segments, followed by PET, and finally the 'other' category, which includes molecular imaging aspects of both SPECT and MRI modalities.

Survey results and observations

In October 2007 Insight Pharma Reports surveyed technical and business practices of individuals involved either directly or indirectly with *in vivo* molecular imaging. A total of 139 people in a variety of organisation types responded to some or all of 19 questions. Some of the observations and conclusions from the survey are:

1. Among the three sectors selected, big pharma has the deepest pockets for expensive molecular imaging technologies (notably PET).
2. Big pharma leads the three sectors in application of molecular imaging to clinical development, especially late-stage development.
3. The commercial biotech sector focuses more on imaging in preclinical development and less on late-stage clinical development, which presumably is often licensed out to big pharma.
4. For both big pharma and commercial biotech, applications of molecular imaging in drug discovery and preclinical development dominate uses in clinical development.
5. Optical imaging is dominant among modalities in all three sectors.
6. PET is used significantly more frequently in big pharma than in the other two sectors?

This article is based on a new report, *Molecular Imaging in Drug R&D and Medical Practice: Technologies, Applications, Markets*, from Insight Pharma Reports, a division of Cambridge Healthtech Institute, in Needham, Mass. To learn more about this report and other Insight Pharma Reports, go to www.insightpharmareports.com. DDW

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