Industry Watch

Medical Imaging in Drug Discovery, Part III

'Whole body' imaging potentially can make fundamental research more useful and help clinicians evaluate new treatments quickly and more effectively. One particular asset to productivity is that because only very low amounts of radiolabeled drug have to be administered for analysis, human studies can be carried out even before the drug is entered into Phase I trials.

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In this, the last in our series of columns devoted to the expanding role of imaging technology in healthcare, we take a closer look at how molecular imaging in small animals — and even in humans — is helping advance and streamline the drug development process.

Why small animals? With *in vivo* imaging, it enables easier demonstration of drug efficacy, or the lack thereof. Also, the chemical derivative that allows for imaging can be unsafe for long-term human health — but basic information on tissue distribution and metabolism can be obtained in animals and then "translated" for use in human research.

Ideally, though, using imaging technology in humans — what is called "whole body" imaging — offers an even faster way to get drugs to the market so that diseases can be treated. Imaging the whole human body is a way to make fundamental research more useful and helps clinicians evaluate new treatments quickly and more effectively. It's safe, non-invasive and is proving increasingly productive for the pharmaceutical and biotechnology industries.

Let's delve deeper into the value of whole body imaging for drug development.

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Imaging the Response to a Drug

First, let's compare the typical way in which drug development unfolds:

Once a target has been identified and a lead compound is identified *in vitro* and in animal models, a toxicity profile is determined. A Phase I study then is undertaken to determine the maximum tolerable dose (MTD), followed by a Phase II study of the compound at its MTD to make an assessment of the drug's efficacy and whether that benefit is sufficiently better than other available treatments to warrant continuing the development process. This takes a long time — Phase II alone usually takes 18 to 24 months — and costs a bundle of money. And then, only if the evidence from Phase II is sufficient to warrant it, the process moves on to Phase III, where the drug's benefits are evaluated under "real-life" conditions.

Much of the crisis in drug development productivity can be traced to the scientific limitations of *in vitro* research. As David F. Horrobin asks in a provocative article published last year, "Does the functioning of cells in culture bear a sufficiently strong relationship to the functioning of cells in an organ *in vivo* such that conclusions drawn from the former are useful in predicting behavior of the latter?" He answers that the *in vitro* system cannot "construct a functional and valid *in vivo* biochemistry," and identifies this as a potential "fatal flaw" (1).

Couple this problem of science with the huge time and expense involved in traditional clinical trials and the crisis of low productivity appears even more desperate. But what if it could be overcome (at least in part) through imaging? Advocates of using this technology in drug development assert that the value will be in doing just that. The idea is that some initial imaging in small animals will allow researchers to predict whether a given drug would work. And if that doesn't do the trick, the efficacy could be assessed — again, using imaging — at a variety of dose levels once the drug has been administered.

With such early measures, researchers reasonably could predict long-term benefits and toxicity, potentially providing an

answer to the crucial question that bedevils drug developers and that today costs tens of millions of dollars to determine: should we pursue this therapy or drop the project?

Today's imaging technologies already are being employed in this way. Growing numbers of researchers are employing nuclear medicine tools to image at the molecular and whole body levels. The tool of choice, at least at this moment, is positron emission tomography (PET), which allows researchers to go beyond small animals and study humans. As Paans and Vaalburg explain, PET is an imaging technology that can "determine biochemical and physiological processes *in vivo* in a quantitative way by using radiopharmaceuticals labeled with positron emitting radionuclides (such as 11C, 13N, 15O and 18F) and by measuring the annihilation radiation using a coincidence technique. This also includes measurement of the pharmacokinetics of labeled drugs and the assessment of the effects of drugs on metabolism. Because only very low amounts of the radiolabeled drug have to be administered — far below toxicity levels — human studies can be carried out even before the drug is entered into Phase I trials. Such studies can provide cost-effective predictive toxicology data and information on the metabolism and mode of action of drugs" (2).

Just where are the savings? With PET, both pharmacodynamic and pharmacokinetic effects of drugs can be evaluated. The metabolic response of cells in the tissue can be measured, allowing researchers to determine the pharmacodynamic effects of a drug in the human body. "By the study of only a few volunteers, the affinity and the selectivity of a new drug for a specific receptor system or subsystem can be assessed" (3).

In pharmacokinetic studies, researchers using PET can obtain details about the metabolic degradation of a drug *in vivo*. They also can predict toxicity in advance of Phase I trials. "Early information can be obtained on the metabolism, the blood-brain barrier penetration, the receptor kinetics and specificity of the compound in humans. This is a major advantage above the present selection of new drugs, which is based upon trial and error and on animal studies" (4).

Industry's — and FDA's — Stance

As drug development inefficiencies were becoming more of a problem in the early 1990s, a small number of people in the pharmaceutical industry — in conjunction with academics — began to explore the potential role of PET in addressing some of the problems. Since then, representatives of industry, academia and regulatory agencies have met in workshops and meetings throughout the world to discuss high-resolution imaging modalities for small animals and how they can be applied to drug development, neuroscience and molecular biology.

Advocates of imaging technology assert that initial imaging in small animals will allow researchers to predict whether a given drug would work and to assess efficacy at a variety of dose levels once the drug has been administered.

In a 1999 article, Richard Frank, senior director of exploratory medicine at Sanofi-Winthrop USA (New York, New York, USA), spoke of some of the early efforts. "Ten years ago, I first became aware of the tremendous drug research potential of PET when I participated in one of the first clinical trials that applied PET in conjunction with a receptor-specific tracer to a drug development problem. By quantifying receptor saturation of a labeled serotonergic agent, we could directly measure how much of the agent crossed the blood-brain barrier during a Phase II trial. Several investigators now are similarly applying PET in new ways to research treatments for cancer, Parkinson's disease and rheumatoid arthritis" (3). Since then, drug development-related use of PET has blossomed.

Just as industry has embraced imaging tools for the promise they offer to help solve the efficiency problem, government regulators also have opened themselves to the possibilities. In March 1996, FDA began an initiative, called "Reinventing the Regulation of Cancer Drugs," and stated that the agency would, "substantially expand the use of accelerated approval processes for cancer treatments, based upon verified and recognized demonstration of objective tumor shrinkage" — meaning medical imaging endpoints. Then, in March of the following year, FDA issued a guidance document that advocated the use of medical imaging endpoints in clinical trials. Three years later, the agency released a report titled "Guidance For Industry: Developing Medical Imaging Drugs and Biologics."

Progress has been made elsewhere in the government. The National Cancer Institute (Bethesda, Maryland, USA), in 1999, issued a request for applications related to scientific rationalization of imaging technologies that stated, "Advances in technology now have made imaging an important, non-invasive tool for the functional or quantitative assessment of biochemical, genetic or pharmacologic activity. Imaging modalities such as magnetic resonance spectroscopy (MRS), positron emission tomography and single photon emission computed tomography (SPECT) are uniquely suited to this challenge. These techniques are ready to be incorporated into early clinical trials of therapeutic agents" (4). And President Clinton, during his last month in office, signed legislation establishing the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health (Bethesda, Maryland, USA).

Industry and regulators are recognizing that the use of imaging in clinical trials will aid in selecting the most appropriate subjects, monitoring disease progression and therapeutic response, and monitoring complications of the

disease or therapy. "In addition to supporting definitive testing in Phase III of drug development for regulatory approval, imaging also facilitates internal decision-making in Phase II about which compounds to prioritize. This includes proof-of-concept studies, dose-selection studies, patient-typing studies, etc. Here, an early readout is particularly valuable…There is a huge upside to rapid decision making in the competitive arena of drug development" (5).

Cancer is a major area of interest for the use of imaging, but it is not the only one. Researchers are using the technology, for instance, to overcome the barriers to developing new psychiatric drugs, which "include an incomplete understanding of the pathophysiology of psychiatric disorders, of the adaptive brain response related to the therapeutic response to a course of treatment of brain penetrance, accumulation and elimination of psychoactive medications and of the dose- and time-dependent interactions of such medications with molecular targets in the brain. *In vivo* brain imaging techniques such as PET, functional magnetic resonance imaging (MRI), SPECT and MRS are emerging as multimodal approaches to understanding these processes in the living human brain…These techniques hold increasingly realized promise to inform the relationship of the brain and mind and, in doing so, to guide the rational development of more efficacious and better tolerated medications" (6). This is but one of many, many examples we could cite.

What Does the Future Hold?

All indications are that molecular imaging will become an increasingly central component of drug development, used in living subjects. In many respects, researchers only have scratched the surface of the possibilities.

One area where the technology is likely to expand and combine with other disciplines is computational cell biology. As the ability to image biological processes in living subjects grows, the data sets could become so complex as to require that researchers employ new tools to interpret what they find. "A fruitful interchange between molecular imaging and the emerging new discipline of computational cell biology will be essential in uncovering the pathways, mechanisms and controls of biological processes and systems as they occur *in vivo*" (7).

David Horrobin makes another case for imaging in whole-animal studies: the crucial need for an understanding not only of the "anatomical layout of biochemical pathways but also of how they interact kinetically." Absent this knowledge, "which in the end can only come from *in vivo* animal studies, then no sense can be made of the information from, for example, cell culture studies or applied human physiology" (1).

Industry and regulators are recognizing that the use of imaging in clinical trials will aid in selecting the most appropriate subjects and in monitoring disease progression, therapeutic response and potential complications.

Imaging can do a lot to help us understand time-dependent responses in humans. The technology can help get us closer to the personalized medicine about which we've written in several previous columns. First, though, it looks as if it can help researchers take a giant leap forward in solving the problem of unproductive drug development.

We think Massoud and Gambhir perhaps put it best: "With luck and perseverance, insights made from these methods may be as useful as those made from telescopes turned on the skies and microscopes focused on cells and tissues. This potential power of molecular imaging to see fundamental biological processes in a new light will not only help to enhance our knowledge and understanding but also should accelerate considerably the rate of discovery in the biological sciences" (7).

From small animals to human trials, molecular imaging will contribute considerably to the development of new pharmaceutical therapies. Could we be nearing the end of timely, costly clinical trials – with no degradation in terms of what we learn about safety and efficacy of new drugs?

References

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