Imaging in Drug Discovery, Preclinical, and Early Clinical Development

Imaging plays an increasingly fundamental role in drug discovery and early development in humans. It is already used routinely in therapeutic areas such as the central nervous system (CNS) and increasingly in oncology, cardiology, and other disciplines. Molecular imaging in drug discovery and development can begin in small rodent models and is becoming increasingly important in nonhuman primate models, to the extent that many of these studies are done in-house by pharmaceutical companies or in collaboration with dedicated academic partners. PET/SPECT neuroreceptor and metabolic imaging, as well as conventional and functional MR imaging, MR spectroscopy, optical imaging, and other techniques, is utilized almost routinely to help establish proof-of-concept/proof-of-mechanism studies for new drugs, especially at the interface between preclinical and early phase 1 studies. Additional imaging is used to help establish the rationale for drug doses for late phase 1 and 2 clinical trials. Finally, imaging can establish measures such as receptor occupancy at the hypothesized biological target indicated in patient populations to further streamline, economize, and accelerate the timing of multicenter trials required before a drug is marketed. Imaging has a tremendous future as the early pivotal measure—often as a biomarker and, hopefully, in some cases with surrogate marker status—for drug development. For nuclear medicine, it represents an important academic role for scientific collaboration.

Imaging Modalities: Therapeutic Areas

Many modalities and approaches are involved in early drug development, but for the purposes of this presentation we will focus mainly on PET and SPECT imaging of receptors as an especially active area. Much of what happens with these molecular imaging modalities in early drug development occurs in the early target phase, at the interface between drug discovery and phase 1 studies. This point in development can be quite exciting—1 day the focus may be on a rodent or primary model and the next the focus may shift to an exploratory Investigational New Drug filing. This kind of development is a part of the mission of molecular imaging specialists in academia, industry, and the government. We have come a long way from the time when people thought that working with the pharmaceutical industry meant doing only phase 3 or 4 studies, charging lots of money, and taking nice trips with no academic value. The new kinds of dynamic studies at the interface of basic sciences and clinical applications are now the bread and butter of nuclear medicine and imaging departments. And as we discover new targets through industry partnerships, these become the basis for our next National Institutes of Health (NIH) or Department of Energy grants.

The example that we will focus on today, molecular imaging of neurotransmitters and receptors, has a long history, with imaging efforts in humans going back to the early 1980s and in animal autoradiography to the 1970s. Today we have the advantage of being able to link together the maturing field of receptor imaging with the even more mature field of metabolism, not just in brain studies but in other areas as well. PET and SPECT receptor imaging is used in proof-of-concept studies in numerous ways. Examples include using an established radiotracer to measure receptor occupancy of a new unlabeled drug, using a new radiotracer to target a receptor not previously established, and measuring D_2/D_3 occupancy for atypical antipsychotic agents. PET and SPECT receptor imaging is also used in proof-of-mechanism studies. Examples included: determining what receptor occupancy is needed for efficacy in future phase 1/2 trials and determining whether a test drug modifies imaging parameters in ways that may lead to understanding the mechanism of action.

Dopamine and other receptors were first successfully imaged in the living human brain by PET and SPECT in the early 1980s, first in the United States and globally only a few years later. Today the list of neuroreceptor systems imaged with PET and SPECT is long and growing daily. The dopamine system is the most studied of the neuroreceptor systems. We can study the precursors for dopamine, packaging and release of dopamine into the synapse, reuptake, and the postsynaptic effect. This provides a rich field for research, because many drugs will work on these areas. Radiolabeling remains a challenge, as ^{11}C or ^{18}F are suitable for only a small fraction of CNS molecules, and labeling with ^{99m}Tc or ^{123}I is even more challenging.

Molecular CNS imaging with PET and SPECT may be considered valuable in 4 main areas that are most useful in engaging pharmaceutical companies in collaboration. These are: (1) providing the therapeutic rationale for drugs; (2) rational drug dosing; (3) radiolabeling of candidate drugs; and (4) studies of the mechanisms of action.

(1) Providing the therapeutic rationale for drugs is among the most important areas of collaboration for academic centers. If we look, for example, at the spectrum of current dopamine pathology studies on in-development therapies in a range of diseases, including schizophrenia, bipolar disease/psychosis, Tourette's, temporal lobe epi-

lepsy psychosis, alcoholism, and restless leg syndrome, we can see that PET and SPECT are providing presynaptic, postsynaptic, and intrasynaptic data that are available by no other methods in neuroscience. Moreover, this spectrum of studies is slowly filling in to provide a therapeutic rationale for a number of disorders, helping us to understand the relationship between neurotransmitters and receptors and pointing to other relationships, such as those between neurologic disorders and environment and genetics. It is fair to say that much of what we do as NIH-funded molecular imaging researchers provides the basis on which pharmaceutical companies come to understand that certain drugs might be useful in specific ways.

(2) PET and SPECT also enhance drug development by providing data for rational drug dosing by measuring in vivo pathology. One example can be found in antipsychotics that block D_2/D_3 receptors. We have known for many years that haloperidol blocks these receptors, but more recent antipsychotics have fewer side effects. The traditional method for evaluating these drugs was to test first in normal volunteers and then in patients to determine optimal dosages. The result would be an occupancy curve against plasma concentrations. This curve provides information about the point at which the receptors are saturated (i.e., the point at which higher dosages are not needed). Today, for drugs for schizophrenia, for example, occupancy as measured by molecular imaging can be correlated directly with an oral dosage administered in patients to provide data about dosing. Studies of receptor occupancy in drug abuse are also providing valuable data. One example of opportunities for collaboration comes from our own work, where we were using ^{11}C-WIN to study baseline and higher occupancy states of cocaine in baboons. At the same time, National Institute on Drug Abuse (NIDA) researchers were doing a multiple-dose study of GBR-12909 in healthy volunteers. NIDA teamed up with Johns Hopkins and the Uniformed Services University of the Health Sciences for a collaborative study looking at the occupancy of the drug as a potential treatment for cocaine abuse. The resulting dose–response curve indicated that GBR-12909 had promise in this setting, and NIDA proceeded to additional studies. In this instance, academia worked with government scientists on a compound that was not on the market but of great interest to the pharmaceutical industry.

PET and SPECT are also being used to assess receptor occupancy for potential treatments for obesity and appetite suppression (e.g., opiate antagonists and cannabinoid 1 antagonists). One example of real benefits realized fairly simply is in an already marketed drug, naltrexone. By looking at the dose-occupancy curve for the drug, the maker determined that this could be used as a longer-lasting therapeutic in combination with another agent.

It is clear in these and other areas that molecular imaging data on drug dosing has extraordinary potential, a potential that is increasingly recognized by the pharmaceutical industry. One unique advantage is that molecular imaging provides the ability to study compounds not only during administration but after cessation of administration. For example, in a study of a single-dose agent, the occupancy over 24 h remained quite high, yet the plasma levels fell off rapidly. This reinforces what seems axiomatic: when looking for something that works in the brain, it is better to assess its effects by looking in the brain than in the plasma.

(3) PET and SPECT are also, as we would expect, useful in radiolabeling of candidate drugs. In the past, a developer may have had a promising drug, with the only limitation being that no available method (mass spectrometry, for example) could visualize it in animals in the very low quantities that might be needed to prepare for phase 1 studies. PET and SPECT provide the capability to verify that radiolabeled compounds bind with receptors to validate studies in animals and humans.

(4) A final fruitful area of molecular imaging research in preclinical and early clinical work is in evaluating the mechanism of action. Often we do not know precisely how a drug works but know that elucidation of this mechanism will serve to expand scientific knowledge about the disease or target area. If we go back to the example of GBR-12909 as a potential drug for cocaine abuse, the point was to use it to reduce the stimulating effects of cocaine and amphetamine. But we needed to understand precisely how this action occurred. Through imaging studies, we found that GBR-12909 not only blocks the action but lowers the initial binding to receptors, which may, in turn, help with cocaine craving. This finding was among the reasons why NIDA is continuing these studies in cocaine users. Although cocaine addiction is quite complex, we now have a better idea of the mechanisms involved and new data on potential ways to treat it.

Challenges in Imaging Biomarkers

One important rule to remember is that imaging neuroreceptor occupancy is necessary for preclinical and clinical studies but is not the same as proving efficacy. One example can be found in partial agonists of dopamine D_2/D_3. As noted previously, we want the new antipsychotics to have fewer side effects, in the hopes that patients will stay on the medication. Studies now indicate that partial dopamine agonists require additional occupancy (above that identified by imaging) for optimal efficacy. A second example can be found in the saga of efforts to develop drugs targeted at the neurokinin receptor subtype NK1, the target of substance P. After attempts to develop analgesics targeted at substance P failed, early reports indicated a distinct mechanism for antidepressant activity by blockade of central substance P receptors (NK1). Numerous NK1 receptor antagonists either have been synthesized or have already been tested in clinical trials. The idea of using them for treatment of affective disorders seemed logical and promising, especially when preclinical studies with a validated radiotracer were successful. The dose curve, supported by PET imaging studies in animals and humans,

indicated receptor occupancy. However, this was followed by repeated demonstrations of lack of efficacy at higher and higher doses. Although tremendous industry investment went into this effort, doubt now currently surrounds the idea that these compounds may become effective antidepressants. One of the challenges, then, is that we cannot know ahead of time what level of occupancy is needed for efficacy.

Other important cautions in thinking about potential imaging biomarkers include the fact that some radiotracers used for disease progression (for example, in Alzheimer's disease and Huntingdon's disease) may be better for initial diagnosis than for monitoring disease with or without therapy. ^{11}C-PiB, for example, may be sensitive in Alzheimer's disease at baseline, but ^{18}F-FDG may provide a clearer assessment of changes over time. In addition, the concern is that many of these amyloid imaging compounds may be useful in cross-sectional diagnoses but the information gained in these diagnoses may not be valuable in changing either the natural history or treatment.

The Radiotracer Clearinghouse: A New Approach for Sharing Biomarkers

A final area of challenge is in intellectual property and sharing of tracers. Too much duplication of effort (e.g., toxicology and dosimetry studies) is devoted to the same limited number of successful radiotracers. Individuals from the American College of Neuropsychopharmacology and Society for Non-Invasive Imaging in Drug Development initiated a concept of sharing in a trusted environment. This is a proposal to create a novel way to share PET radiotracers among academic and industry scientists even before full public disclosure, because of concerns about trade secrets or even under the FDA research exemption to use patented or publicly known radiotracers. This grew out of discussions between industry research and development leaders and academic PET investigators in the CNS area.

This clearinghouse would: (1) provide a central database of companies, academic centers, and radiotracers; (2) provide a neutral and confidential intermediary model to encourage collaboration among companies and between companies and academic PET centers; (3) establish a tier-based annual fee system of membership and tiered charges for involvement by clearinghouse staff; (4) meet the requirements of 4 case examples developed by the planners and follow templates developed for other technological development efforts; and (5) provide a mechanism to share radiotracers globally across any academic or government PET center and industry, with the capability to facilitate public disclosure as well as confidential interactions for all targets and therapeutic areas. Many of us believe that these clearinghouse principles are critical to the development of new research tools and in the application of imaging technology to drug development. They can be implemented within a standalone nonprofit enterprise or incorporated into another entity. This interaction can be global and is not dependent on specific countries or regions but remains respectful of local cultures and regulations.

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Imaging Biomarkers, An Industry Perspective

The imaging industry, pharmaceutical companies, the U.S. Food and Drug Administration (FDA) and other government agencies, and payers all look to imaging as critical to personalized medicine, but each from a different and sometimes mutually exclusive viewpoint. An emphasis on drug development and qualified biomarkers obscures the need of the imaging industry to obtain new validated (commercial) products. Clearly both are needed, but the current regulatory architecture is not well described and presents unnecessary risk. This presentation describes some of the issues that qualified and validated imaging biomarkers face and suggests a new architecture that may meet the needs of all parties.

The FDA recognizes 2 classes of biomarkers: those that predict the presence of disease or characterize disease and those that predict response to therapy. A qualified imaging biomarker is one that is established for some aspects of drug development providing data on safety or efficacy but that does not have specific labeling as an approved drug. Examples are unsealed sources for radiation dosimetry or the Response Evaluation Criteria in Solid Tumors (RECIST)/World Health Organization criteria for tumor response. A validated imaging biomarker is an approved drug with the corresponding indication to assure or improve safety and/or efficacy. An example is whole-body biodistribution assessment in Zevalin and Bexxar. It is important to note that commercialization is tied to validation.

Every group involved in drug or agent development has different goals and different ways of meeting these goals. Companies who develop imaging (diagnostic agents) want faster, cheaper successful clinical trials, as do companies who develop therapeutic agents. Diagnostic imaging companies would like to get from the validation side through to commercialization as quickly as possible, whereas the