Molecular Imaging to Biomarker Development in Neuroscience

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CNS drug candidates fail approval in over 90% of the cases due to poor targeting, lack of efficacy, and/or unacceptable side effects. *In vivo* imaging offers a pathway to derisk drug molecules at each stage of development, but more research and development is needed to fully realize this potential. The greatest activity is in the use of target biomarkers, but those for disease mechanism, efficacy, and toxicological effects are under study and urgently needed. Many of the biomarker tracers can later be developed as new diagnostic imaging agents and then used to guide individual molecular therapy. Realization of this goal will require ongoing collaborative research and development among universities, pharmaceutical companies, biotechnology, the contract research organization (CRO) industry, diagnostic companies, and producers and distributors of radiopharmaceuticals. During the past decade there has been a progressive merger of the interests of the pharmaceutical industry and academia in the area of molecular biomarker imaging in human brain disease. Historically, academia has been more focused on disease mechanisms, etiology, diagnosis, and treatment monitoring. The pharmaceutical industry has concentrated more on medication development, drug pharmacokinetics, and surrogate treatment end points. In the era of personalized medicine, these interests have evolved to a continuum where the knowledge of diagnosis and molecular mechanism of disease from imaging not only guides new medication development but also is beginning to direct individualized drug choice and dosage.

Key words: **drug discovery; molecular; biomarker; positron emission tomography; receptor occupancy; diagnostic**

The evolution of molecular imaging toward biomarker development has created new opportunities for collaborative research and development between academia and the pharmaceutical industry, and also opportunities for the development of new commercial diagnostic radiopharmaceuticals. The benefits to both parties are significant. Academia provides the scientific and imaging infrastructure resources for drug radiolabeling and the pharmaceutical companies provide the chemical matter for radiotracer development, which can later be used for new scientific studies of molecular mechanisms of disease and significant new grant and foundation funding (Fig. 1).

The case for collaborative research and development is particularly compelling for CNS drugs, since a greater percentage of CNS drugs fail efficacy trials compared to other categories (92% vs. 89%) and the costs of bringing a drug to market is twice that for other classes ($1.6 M vs. $800 M). The ability to derisk drug candidates in early-stage imaging studies by abandoning those with poor bioavailability and pharmacokinetic properties, and channeling resources into those with a higher likelihood of achieving the desired efficacy end points in later-stage clinical trials provides a high value for reducing the costs and accelerating drug development and approval. Additional research and development will lead to the use of some of these new radiotracers as supplementary or surrogate end points in the efficacy trials

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Ann. N.Y. Acad. Sci. 1144: 251–255 (2008). © 2008 New York Academy of Sciences.
doi: 10.1196/annals.1418.027

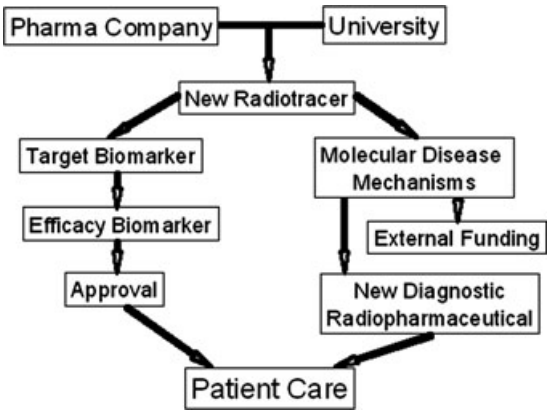

Figure 1. Flowchart for pharmaceutical–university collaboration in biomarker research and development. Research and development can enhance patient care by bringing together better understanding of the molecular basis of disease, new biomarkers, and molecular diagnostics.

themselves. Finally, this continuum will extend to the development of the same tracers as commercial diagnostic radiopharmaceuticals that will eventually dictate the use of a specific drug and dose for individualized treatment, and will be used to monitor the treatment response.

A biomarker is "a characteristic that is objectively measured as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention." There are several motivating factors for the adoption of in vivo biomarkers. A biomarker can replace a distal end point with a more proximal one that can be measured earlier, permitting the shortening of some clinical trials. An *in vivo* biomarker can often be measured were easily or more frequently than conventional end points and often with higher precision. An objective biomarker may also be less affected by co-morbid disorders and standard of care treatments that cannot be terminated in a clinical trial. All of these factors may result in reduced trial sample size, faster decision making, and cost savings.

There are several types of imaging biomarkers that are being developed.[1] The three primary types are for drug targeting, for effect on disease mechanism, and for efficacy. Drug-targeting studies are conducted by labeling the candidate drug molecule or by competing the unlabeled drug against a radiolabeled drug analogue of similar pharmacological specificity. Targeting studies are used to demonstrate drug candidate's brain bioavailability and whether the drug reaches its intended target, such as a receptor or enzyme. When data from biomarker targeting studies are quantified, they can be used to guide the dose for later efficacy trials by measuring percent receptor occupancy or enzyme inhibition.

Some biomarkers designed to demonstrate whether a specific disease mechanism is altered following therapy. Unfortunately, the mechanisms of most neurological and psychiatric disorders are unknown. Parkinson's and Alzheimer's diseases are exceptions, in that the role of dopamine loss and amyloid deposition, respectively, are well described.[2] For other brain disorders, however, including schizophrenia, depression, anxiety disorders, and substance abuse, detailed mechanisms are incompletely understood. As molecular imaging research continues in these disorders, new knowledge will aid the development of new drugs and will provide new mechanism biomarkers.

Validated efficacy biomarkers will provide the greatest benefit to drug development by providing objective disease modification end points, and thereby shorten clinical trials and reduce costs. The highest level that an efficacy biomarker can achieve is that of a surrogate end point: *a laboratory or physical sign that is used in the therapeutic trials as a substitute for a clinically meaningful end point; that is a direct measure of how a patient feels, functions or survives; and that is expected to predict the efficacy of the therapy.* F-18 fluorodeoxyglucose (FDG) is increasingly used for oncologic clinical trials, including for brain gliomas, but the development of efficacy and surrogate end points for the majority of brain disorders remains incomplete.

While target, mechanism, and efficacy biomarkers are useful for studying and derisking new drug candidates as they approach clinical trials, they do not directly assess the

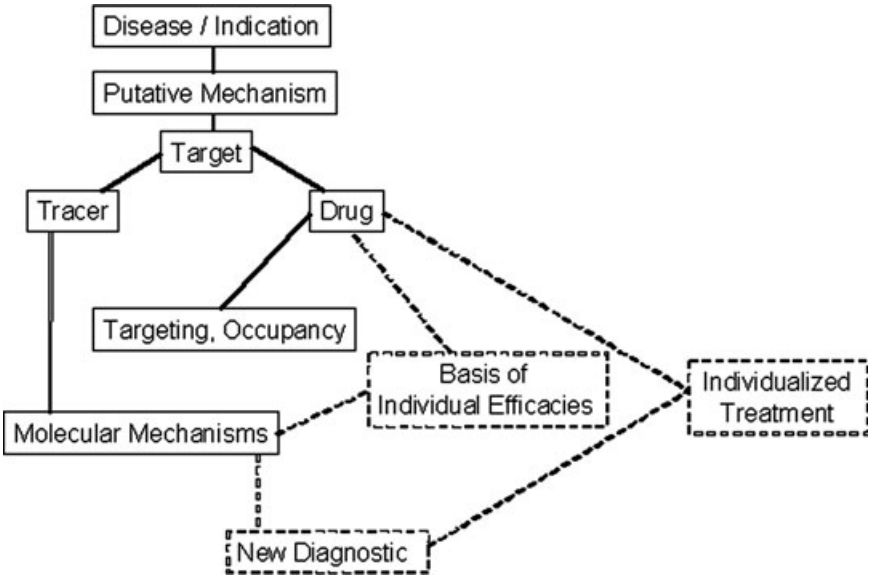

Figure 2. A pathway to achieving individualized treatment. The *solid lines* show what has already been achieved for some CNS diseases, and the *dotted lines* show where advances are still needed.

potential for toxicological side effects. The approval prospects for a new drug can be adversely affected by the presence of side effects, even though efficacy is well demonstrated. An example of this is the clinical trial of the successor to Pfizer's Lipitor, torcetripib. Torcetribip worked well in regard to a number of targeting, mechanism, and efficacy biomarkers but was associated with an increased death rate in the pivotal clinical trial. Accordingly, more effort is needed to develop better toxicological biomarkers to supplement those for efficacy.

Research and development in the areas just referenced will ultimately lead to the approval of new commercial diagnostic imaging agents. This will occur through collaborative research among the pharmaceutical, biotech, academic, contract research organization, and radiopharmaceutical production and distribution domains. Although significant regulatory hurdles remain in the approval of new diagnostic imaging agents, the rationale for coupling *in vivo* diagnostics, *in vitro* diagnostics, and therapeutics continues to strengthen. As targeted therapies continue to be developed, the use of new molecular biomarkers will also provide prognostic value as they are used not only to monitor the therapeutic response but also to predict it (see Fig. 2).

There are a number of molecular radiotracers for brain imaging that can also be used as imaging biomarkers. These include pre- and postsynaptic radiotracers for dopamine, serotonin, noradrenalin, cholinergic, opiatergic, GABA-benzodiazepine, and several other neurotransmitter systems. In Alzheimer's disease, amyloid imaging using C-11 PIB (Pittsburgh compound B) is under very active study as mechanism and efficacy biomarkers for anti-amyloid therapies.[3] As a result of the increasing role of neuroinflammation in many diseases, including Alzheimer's and Parkinson's disease, peripheral benzodiazepine receptor imaging using C-11 PK11195 and related compounds is also receiving renewed attention.[4] Nevertheless, given the fundamental role of inflammation in many neurodegenerative disorders, new inflammatory tracers are needed.[5]

The most widespread use of the previously referenced radiotracers is in the area of drug targeting, where imaging can be used to demonstrate and quantify drug bioavailability.

This approach alone is, however, adequate, as the example of neurokinin-1 (NK-1) receptor occupancy imaging using F-11 SPARQ aptly demonstrates.[6] In this study conducted by Merck, NK-1 receptor targeting was well quantified and the drug dose needed to achieve the needed receptor occupancy of approximately 90% was determined. Nonetheless, in the clinical trial in primary affective disorder no efficacy compared to placebo treatment was observed. This example demonstrates that targeting biomarkers alone are inadequate to fully characterize a drug's profile and the likelihood of eventual approval.

A recent example of a drug-targeting study involves naltrexone's inhibition of mu- and delta-opioid receptors. Naltrexone is currently used to treat alcohol dependence by inhibiting the opioid-mediated craving caused by alcohol. Although naltrexone is efficacious in many alcohol-dependent subjects, the clinical response varies widely. In order to examine whether the clinical response variability is related to inhibition of mu- and/or delta-opioid receptors, Weerts *et al.* measured the inhibition of mu- and delta-opioid receptors after 50 mg naltrexone.[7] Whereas mu receptor binding was completely inhibited, delta receptor binding was only partially inhibited. Furthermore, there was high variability among subjects in the degree of delta receptor inhibition, and accordingly, the variability in delta receptor inhibition could be responsible for the variability in naltrexone efficacy. This result also suggests that selective delta receptor antagonists may be useful in the treatment of alcohol dependence.

Another application of opioid receptor imaging is in the study of cocaine addiction. Mu-opioid receptors have previously been shown to be upregulated in proportion to craving in various limbic brain regions in cocaine addicts.[8] The time course of the upregulation has also been studied up to 90 days of monitored abstinence.[9] Subjects were then monitored for up to one year after monitored abstinence to determine the time to relapse and the severity of the relapse. This phase of the study demonstrated that the magnitude of the change in mu receptor binding was correlated with the time to and severity of relapse.[10] Subjects in whom upregulated regional mu binding returned toward normal levels had a longer time to relapse and diminished severity of the relapse to cocaine self-administration. Importantly, regional brain mu receptor binding at 7 days abstinence was also correlated to relapse even when the relapse occurred over one year after the day 7 PET scan. This finding suggests that mu receptor binding could play a diagnostic role in the future by identifying subjects who are likely to experience an early relapse and therefore would require more aggressive treatment. A similar study in treatment-seeking cocaine addicts is currently under way. The preliminary results demonstrate that opioid receptor imaging pretreatment is correlated with the treatment response as measured by cocaine and metabolite levels in urine, further making the case for a diagnostic utility (Frost *et al.*, unpublished).

In summary, *in vivo* molecular imaging has become critically important for the development of new biomarkers. These biomarkers fall into the broad categories of target, mechanism, efficacy, and toxicological, diagnostic and prognostic. The greatest use of biomarker imaging is in the area of targeting, but new efficacy and surrogate end-point biomarkers are urgently needed. The next logical extension is then to develop new commercial diagnostic tracers, which will greatly advance individualization of treatment for brain diseases.

Conflicts of Interest

The author declares no conflicts of interest.

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