It is true that much PET imaging will be performed by radiologists in private practice who may or may not be interested in the underlying mechanisms whereby pharmaceuticals are concentrated or, indeed, what underlies the specific application to individual disease types. In one way it is a good thing that this is true, because completely trained individuals such as nuclear medicine physicians are not numerous enough to meet the demand for the rapidly expanding applications that we foresee with PET/CT. However, the academic disciplines of imaging require its clinician scientists and expert specialists to understand the underlying biochemistry and the ways in which it might be applied to assist in the management of patients. In order to develop new methodologies and new molecular imaging methods, a well-trained cadre of individuals will be needed with a greater depth of understanding of molecular medicine as it applies to imaging.

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Steven M. Larson, MD
Chief, Nuclear Medicine and Vice Chair for Research
Department of Radiology
Memorial Sloan–Kettering Cancer Center
New York, NY

Molecular Imaging: A Tool for Developing Central Nervous System Drugs

Over the last decade, large drug companies have developed an interest in imaging, particularly with regard to the evaluation of drugs affecting the central nervous system (CNS). As an example of this application, Merck & Co., Inc. has created an imaging division with more than 90 employees and multiple high-level instrumentation foci, including PET/CT, SPECT/CT, MR imaging, and MR spectroscopy. The main focus of this program is on CNS drug development for use in animals and humans. The rationale and application of these development efforts have been described in several publications (*1–5*).

Topical Questions

Alzheimer's disease affects a large proportion of the population. What is the role of imaging in evaluating Alzheimer's disease and in the development of new CNS-based drugs? In particular, what is the role for agents (such as ^{18}F-PIB) that specifically image beta amyloid deposits?

As part of the July 2006 issue of *Nature Medicine*, a group of 32 experts gave their opinions about advances that were important to an understanding of Alzheimer's. In a summary article on "Pinpointing plaques with PIB," Kaj Blennow and Henrik Zetterberg discussed possible applications for imaging beta amyloid aggregation in the brain. Among the potentially useful applications would be differentially identifying the first clinical phase of Alzheimer's disease from isolated memory dysfunction (mild cognitive impairment [MCI]). About 40%–60% of individuals with MCI will develop full-fledged Alzheimer's disease. Although some individuals with MCI may have increased uptake of PIB, stratifying patients according to the degree to which they have PIB uptake may be a way to differentiate a population likely to develop Alzheimers disease. This would be useful for testing drugs that may have potential in Alzheimer's disease.

We now know individuals may have distinct metabolic patterns for key enzymes affecting dopamine metabolism, such as monoamine oxidase inhibitors, and that these differences may play a role in addiction. Do individual variations in metabolism play major roles in other neurotropic drugs, and have PET and MR imaging facilitated a better understanding of the chemical basis for common mental illness and neurologic dysfunction? In developing

CNS drugs, what are the main benefits that can be accrued from radiotracer studies of the drug itself? Are there any applications and potential benefits from pharmacodynamic assessment in patients being treated with these drugs using imaging procedures?

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P. David Mozley, MD
Senior Director, Imaging
Merck Research Laboratories
West Point, PA

What Is the Role of Molecular Imaging in the Management of Cardiac Disorders?

Recent progress in the knowledge of the molecular-genetic mechanisms in cardiovascular disease as well as technological development of new imaging strategies has led to the application of new biologically based approaches. Methods are actively being developed for controlled gene delivery to the cardiovascular system using novel gene constructs. Moreover, gene expression can be controlled and imaged using cell-specific, drug-controlled expression systems.

In contrast to direct, targeted imaging paradigms, indirect molecular imaging is more complex and involves multiple components. "Reporter imaging" is an example of an indirect imaging strategy. This paradigm includes a marker/reporter gene and a marker/reporter probe. Several groups have been exploring this approach in the evaluation of the cardiovascular system (*1–4*). The reporter gene product can be an enzyme that converts a reporter probe to a metabolite that is selectively trapped within transduced cells. The main advantage of this approach is the enzymatic amplification of the probe signal that facilitates imaging of the magnitude and location of reporter gene expression.

Another important novel imaging paradigm is the imaging of molecular markers and biological pathways that give insight into the pathogenesis and progress of diseases and assessment of therapeutic intervention. These include novel imaging strategies for heart failure, thrombosis, apoptosis, atherosclerosis, and angiogenesis. Several specific cardiovascular applications for molecular imaging are being investigated, including the imaging of the angiogenic process targeted at vascular endothelial growth factor (VEGF) (*5*) and αvβ3 integrins (*6*), matrix metalloproteases (MMP), apoptosis (*7*), tracking stem cell therapies (*8*), and imaging atherosclerotic plaques and vascular injury (*9*).

Imaging of Angiogenesis

Angiogenesis represents the formation of new capillaries by cellular outgrowth from existing microvessels and occurs as part of the natural healing process after ischemic injury (*10*). The angiogenic process is a complex multistep phenomenon that involves many stimuli, growth factors, and interactions between multiple cell types (*11*). Favorable conditions or molecular events associated with the initiation of the angiogenic process are potential imaging targets. This includes evaluation of the altered expression of αv integrins (αvβ3, αvβ5), VEGF receptors (in particular VEGF R2 and neuropilin-1), and fibroblast growth factor (FGF) receptors (FGF R1 and syndecan-4), among others.

VEGF receptors are reasonable targets for imaging mediators of ischemia-induced angiogenesis. ^{111}In-labeled $VEGF_{121}$ was evaluated in a model of hindlimb ischemia (*5*), an approach that takes advantage of the specificity of $VEGF_{121}$ for hypoxia-inducible endothelial cell (EC) VEGF receptors. However, this approach may be limited, in part, by the total $VEGF_{121}$ receptor density and the retention of ^{111}In-$VEGF_{121}$ in other critical organs. Additional studies in more clinically relevant models will be required to validate the concept of angiogenic receptor labeling as a clinically useful imaging approach.

The αvβ3 integrin is expressed in angiogenic vessels and is known to modulate angiogenesis and, therefore, represents another potential novel target for imaging angiogenesis. Haubner et al. (*12–14*) reported the synthesis and characterization of a series of radiolabeled αvβ3