Molecular Imaging: A Primer for Interventionalists and Imagers

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The characterization of human diseases by their underlying molecular and genomic aberrations has been the hallmark of molecular medicine. From this, molecular imaging has emerged as a potentially revolutionary discipline that aims to visually characterize normal and pathologic processes at the cellular and molecular levels within the milieu of living organisms. Molecular imaging holds promise to provide earlier and more precise disease diagnosis, improved disease characterization, and timely assessment of therapeutic response. This primer is intended to provide a broad overview of molecular imaging with specific focus on future clinical applications relevant to interventional radiology.

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Abbreviations: CEA = carcinoembryonic antigen, FDG = fluorodeoxyglucose, HSV1-tk = herpes simplex virus type 1 thymidine kinase, MMP = matrix metalloproteinase, NIR = near-infrared, PET = positron emission tomography, SPECT = single photon emission computed tomography, VEGF = vascular endothelial growth factor

IN this era of molecular medicine, our approach to patient care is evolving as disease is increasingly being defined by underlying molecular and genomic aberrations rather than by clinical signs and symptoms alone. Molecular imaging is an emerging diagnostic discipline that aims to visually characterize normal and pathologic processes at the cellular and molecular levels in living organisms (1–4). Broadly multidisciplinary, molecular imaging incorporates methods and concepts from molecular and cell biology, imaging sciences, chemistry, high-throughput biology (eg, genomics, proteomics), nanotechnology, pharmacology, and bioinformatics (1,5–7). It is through molecular imaging that radiology is expected to play a critical role in advancing molecular medicine and potentially revolutionize patient care and biomedical research (8,9).

The potential benefits and applications of molecular imaging stem from two fundamental paradigm shifts, one clinical and the other preclinical. Conventional clinical imaging, as practiced by the modern radiologist, generally relies on macroscopic anatomic and/or physiologic variations for disease diagnosis and assessment. Such morphologic changes are often nonspecific and late phenotypic manifestations of underlying molecular derangements (1,2). By contrast, molecular imaging exploits the use of directed imaging probes to sense the specific molecular alterations underlying diseases rather than downstream end effects at the tissue or organ level. This shift in focus from the nonspecific morphologic to the more specific molecular allows for earlier and more precise disease diagnosis, improved disease characterization, and more meaningful monitoring of disease progression. Moreover, imaging at the molecular level also confers patient specificity; thus, molecular imaging stands to greatly facilitate the practice of personalized medicine in predicting therapeutic response and guiding treatment selection (10). Although the clinical potential of molecular imaging has yet to be realized, several human trials of molecular imaging are under way (11–13).

The potential impact of molecular imaging in biomedical research is equally promising. Although past decades have witnessed explosive growth in our understanding of the fundamental basis of physiology and disease, it has become clear that current paradigms of biomedical investigation have inherent limitations. Traditional in vitro research employs a reductionist approach whereby events under investigation are extracted and studied in artificial environments (eg, cell culture studies). This is problematic because biologic processes rarely occur in isolation and are instead mediated through a complex and dynamic interplay of gene expression, signaling pathways, environmental factors, and inherent feedback mechanisms. Therefore, molecular

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Table 1
Attributes of Molecular Imaging Modalities (1,2)

Modality	Sensitivity	Spatial Resolution	Temporal Resolution	Penetration Depth	Cost
SPECT	Medium	Low	Low	High	Medium
PET	High	Low	Low	High	High
MR imaging	Low	High	High	High	High
US	Medium	Medium	High	Medium	Low
Optical imaging	High	Low	High	Low	Low

imaging, in interrogating molecular phenomena in living individuals, preserves the context of whole biologic systems and enables the transition from a reductionist to an integrative and holistic approach to research (14). In studying disease in physiologically intact environments, molecular imaging assays are therefore more predictive and relevant. This technology also broadens the capabilities of in vivo research. Because molecular imaging interrogates events remotely and noninvasively, analyses can be performed in real time with minimal disturbance to the model system, allowing for continuous observation of dynamic processes. For example, whereas traditional in vivo temporal profile studies required animals to be serially killed at fixed time points to obtain tissue for in vitro analyses, molecular imaging enables real-time monitoring of molecular phenomena through repetitive imaging of a single animal. These distinct advantages, combined with the commercial development of dedicated small-animal imaging instrumentation, have driven the application of molecular imaging tools in the preclinical arena. Imaging of experimental small animal models, usually mice, has been rapidly adopted into the basic science research of dynamic biologic processes such as hypoxia (15), inflammation (16), apoptosis (17), angiogenesis (18), tumorigenesis (19), and gene expression (20,21). More translational applications include stem cell trafficking (22) and monitoring of the distribution and efficacy of novel therapeutic moieties (23). The potential to streamline and accelerate drug discovery and development is perhaps one of the most promising applications of molecular imaging and has garnered considerable interest from academia and industry (23–25).

Interdisciplinary collaborations form the essential foundation for the continued advancement of molecular imaging. Naturally, active engagement by physicians will be critical for successful clinical translation of this novel technology (26). The goals of this communication are to provide a basic introduction to molecular imaging and to stimulate discussion among interventional radiologists about whether and how it could be incorporated into future practice. This review begins with an overview of the imaging modalities used, followed by a discussion of basic molecular imaging approaches. To conclude, specific applications in cardiovascular diseases and oncology are detailed. Because the roots of molecular imaging are in molecular biology, readers are referred elsewhere for a review of molecular biology terminology and concepts (27–31). Several other in-depth reviews of molecular imaging are recommended for further reading (2,4,32–35).

IMAGING MODALITIES

Molecular imaging encompasses a broad set of technologies that couple imaging modalities and contrast agents with molecular specificity. Analogous to stains used in histopathology, these agents, called molecular probes or tracers, consist of a signaling component that emits a detectable signal and a targeting component that confers localization. This latter component can be a peptide, receptor ligand, enzyme substrate, oligonucleotide, or antibody. The imaging instrumentation must then be able to remotely detect this signal with sufficient spatial resolution and sensitivity. Modalities used in molecular imaging include positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance (MR) imaging, optical imaging, and ultrasound (US). These modalities differ in terms of spatial resolution, temporal resolution, sensitivity in probe detection, depth of signal penetration, availability of biocompatible molecular imaging agents, and, of course, cost. Each has its unique advantages and disadvantages, and the choice of imaging system ultimately depends on the question to be addressed. **Table 1** summarizes the characteristics of each modality.

Nuclear Imaging

Many argue that nuclear medicine specialists have been practicing molecular imaging since ^{131}I was first used for thyroid imaging in the 1940s. Indeed, PET and SPECT are routinely used clinically and are the most prevalent molecular imaging modalities to date. Hundreds of nuclear imaging probes have been developed. They include radiolabeled enzyme substrates, receptor ligands, antibodies, drugs, and oligonucleotides (36). Examples of U.S. Food and Drug Administration–approved nuclear probes for SPECT and PET include the ^{111}In–labeled octreotide analogue Octreoscan (Mallinckrodt Medical; Hazelwood, MO) (37) and the ^{18}F–labeled glucose analogue ^{18}F-fluorodeoxyglucose (FDG), respectively.

Nuclear imaging modalities remotely sense molecular events by detecting radioactive emissions from targeted radionuclides. PET specifically detects pairs of coincident γ-rays that result from positron/electron collisions after positron emission. Common positron-emitting isotopes include ^{18}F, ^{11}C, ^{13}N, ^{15}O, and ^{124}I (2,36). SPECT, by contrast, detects γ-rays directly from γ-emitting isotopes such as ^{99m}Tc, ^{111}In, ^{123}I, and ^{131}I (2).

Nuclear medicine modalities have been at the forefront of molecular imaging because of their high intrinsic sensitivity, their unlimited depth pen-etration, and the relative ease of radiolabeling molecular probes (38). PET is superior to SPECT for imaging molecular processes because it is 10 –100 times more sensitive and because positron-