Molecular imaging aims at sensing specific molecular targets, fundamental biological processes, and certain cell types in living subjects. An integrative discipline rooted in the biological, chemical, and imaging sciences, molecular imaging has broad applications in biology and drug discovery and increasingly within cardiovascular disease.

Before discussing key factors spurring the growth of this field, we first briefly review 2 essential components of this technology: imaging agents and imaging hardware.

**Imaging Agents**

Molecular imaging requires highly sensitive and specific imaging agents. Such agents incorporate 2 key factors: (1) a signal detection compound and the corresponding imaging hardware platform and (2) an affinity ligand that recognizes the intended molecular or cellular target. Favorable targets include those with established biological and clinical importance in a disease of interest, as well as targets with inherent signal amplification potential such as internalizing receptors or enzymes. Inaccessible and low-abundance targets (DNA, RNA, sparsely expressed proteins) present greater challenges, particularly in a noninvasive, clinical setting.

Signal detection compounds include radioisotopes for positron emission tomography (PET) and single-photon-emission computed tomography (SPECT) imaging, paramagnetic (gadolinium)/superparamagnetic (iron oxide) agents for magnetic resonance imaging (MRI), fluorochromes for near-infrared fluorescence imaging, and microbubbles for ultrasound imaging. Certain agents can exhibit unique physical changes favorable for signal amplification when spaced close together (eg, quenching of fluorochromes or augmented relaxivity of magnetic substrates). These tags can form the basis of imaging agents with inherent chemical amplification capabilities. Amplification strategies generally enable higher target-to-background ratios, a key strategy for developing sufficiently sensitive agents for clinical use.

Affinity ligands confer molecular or cellular specificity for the target of interest. The application of novel ligand screening methods, emerging new chemistries for conjugation and signal amplification, and nanotechnology have fostered substantial growth in ligand development. From a clinical perspective, qualities of an ideal ligand include (1) favorable kinetics to allow sensitive and fast detection, a particularly important consideration in the evaluation of acute thrombotic syndromes; (2) high sensitivity for its molecular target by using 1 or more signal amplification strategies; (3) a high degree of specificity for its molecular target; and (4) the ability to be readily conjugated to a range of signal detection compounds and still remain efficient as a targeting agent.

Initial cardiovascular molecular imaging studies primarily used radioisotope-derivatized monoclonal antibodies. Although specific, their larger size did not permit fast on/off rates and produced high target-to-background ratios in vivo. More efficient ligands now use smaller molecules such as antibody fragments, peptides, or carbohydrates derived from biochemical or cellular screens. Newer efforts use screening methods such as phage display, nanoparticle libraries, or diversity-oriented synthesis. Additional considerations for reporter agents include whether their signal moiety or affinity ligand supports multivalency, defined as the conjugation of multiple ligands to the signal moiety or the conjugation of multiple signal compounds to an affinity ligand. Multivalent approaches can facilitate delivery of high payloads of signal compounds at the target, dramatically increasing the sensitivity of the agent. Growth in imaging reporters has particularly capitalized on developments in nanotechnology because nano-scale scaffolds and materials are well-suited to support multivalency for affinity ligands and colinked therapeutic molecules. From the comparatively large number of new agents anticipated in the next 5 years, several candidates should emerge as promising clinical imaging agents (the Table) on the basis of their high sensitivity, molecular specificity, lack of toxicity, favorable pharmacokinetics, cost, and relative ease of synthesis.

**Imaging Hardware Platforms**

The choice of imaging platform for a clinical molecular imaging study depends on a variety of factors, including the inherent sensitivity, spatial and temporal resolution, depth penetration, range of detection systems (noninvasive, invasive), radiation exposure, throughput, cost, and the availability of high-quality imaging agents for the desired molecular target. For example, assessing a primary tumor in cancer imaging often presents a much larger, static target than a coronary atheroma. Cardiovascular imaging studies thus require high-resolution strategies for both vascular (eg, athero-
sclerosis detection) and myocardial (eg, differentiating endo-
cardium from epicardium) applications that must also
overcome cardiac and respiratory motion and blood flow. In
addition, favorable platforms allow concomitant assess-
ment of cardiovascular anatomy and function. A number of prom-
ising modalities are available for clinical cardiovascular
molecular imaging, either as standalone or fusion technolo-
gies, such as MRI9 and integrated nuclear/computed tomog-
raphy (CT) systems (PET/CT, SPECT/CT).50 Emerging mo-
dalities include optical imaging (in particular, intravascular
near-infrared fluorophore [NIRF] reflectance,51 and fluores-
cence-mediated tomographic imaging52), as well as integrated
PET/MRI53 and fluorescence-mediated tomography inte-
grated with CT, MRI, or ultrasound.

**Addressing Unmet Needs**

Why might molecular imaging prove clinically useful? Could
such modalities provide useful information beyond that of-
fered by anatomy- or physiology-based imaging? The answer
might be yes, because most diseases have an underlying
biological basis that is not visualized by traditional imaging
methods. Molecular imaging should prove a natural adjunct
to personalized medicine by helping to tailor drug selection to
an individual’s proteome and genome.54,55 Imaging of impor-
tant molecular targets could transform clinical management
in the following situations.

**Diagnosis and Risk Stratification**

Several important questions remain unanswered in the current
practice of clinical cardiology, among them the following.
Which patients harbor high-risk atherosclerotic plaques that
will ultimately cause myocardial infarction or stroke? Are
there patients more likely to benefit from fibrinolysis in
life-threatening thrombotic syndromes? Which post–myocar-
dial infarction patients will develop pathological ventricular
remodeling and rapid progression to heart failure? Direct
visualization of the underlying biology in the diseased tissue
may identify patients at high risk for cardiovascular compli-
cations, allowing the clinician to tailor management on the
basis of risk. Specific examples of this capability in athero-
sclerosis, thrombosis, and myocardial infarction are discussed
in the next section.

**Selection and Efficacy Assessment of
Molecule-Based Therapeutics**

Many pharmaceuticals target specific molecules, cells, or
biological processes. At present, the selection of such treat-
ments depends on population-based studies or randomized
clinical trials. Although quite powerful, such approaches do
not routinely assess the biological variability of the disease
process in individual patients. For example, do patients with
nonischemic cardiomyopathy benefit from the potential anti-
flammatory effects of statin therapy?56 Perhaps myocardial
imaging of statin-associated reductions in inflammation (as in
atherosclerosis25) could identify patients most likely to ben-
efit. This new approach to targeting therapeutic agents will
likely expand as new imaging agents and molecule-based
therapeutics enter the clinic.

**Conversion of Invasive Diagnostic Tests to
Noninvasive Studies**

Increased diagnostic sensitivity afforded by molecular imag-
ing studies could offer noninvasive alternatives to invasive
tests. As an example, endomyocardial biopsy is the reference
standard to diagnose cardiac allograft rejection, but in addi-
tion to being invasive, it samples only a limited region of the
ventricle. Sensitive, noninvasive methods to image cell death
via annexin V SPECT imaging57 or yet-to-be-developed
agents or leukocyte infiltration via nanoparticle-enhanced
MRI58,59 could provide a safer, more comprehensive option to
assess transplant rejection and antirejection therapies. As
another example, noninvasive visualization of left atrial
thrombi via fibrin-targeted MRI60 might prove an attractive
option to transesophageal echocardiography before urgent

**Table: Clinically Promising Molecular Imaging Agents in Cardiovascular Disease (Partial List*)**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Platform</th>
<th>Clinically Tested?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNPs (iron oxide)29–33</td>
<td>Cellular inflammation (Mac-&gt;SMC, EC)</td>
<td>MRI</td>
<td>Yes (40 patients)</td>
</tr>
<tr>
<td>18FDG34–38</td>
<td>Glucose transporter-1, hexokinase</td>
<td>PET</td>
<td>FDA approved</td>
</tr>
<tr>
<td>99mTc-annexin39,40</td>
<td>Apoptosis/macrophages/intraplaque hemorrhage</td>
<td>SPECT</td>
<td>Yes (24 patients)</td>
</tr>
<tr>
<td>99mTc-interleukin-241</td>
<td>Lymphocytes</td>
<td>SPECT</td>
<td>Yes (25 patients)</td>
</tr>
<tr>
<td>ProSense14,42</td>
<td>Cysteine protease activity</td>
<td>NIRF</td>
<td>Planned</td>
</tr>
<tr>
<td>Paramagnetic nanoparticles63,44</td>
<td>Angiogenesis (integrin αβ3)</td>
<td>MRI</td>
<td>Planned</td>
</tr>
<tr>
<td>Thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99mTc-aptidide45,46</td>
<td>Platelet glycoprotein IIb/IIIa receptor</td>
<td>SPECT</td>
<td>FDA approved</td>
</tr>
<tr>
<td>EP-2104R47</td>
<td>Fibrin</td>
<td>MRI</td>
<td>Yes (76 patients)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99mTc-NC10/69248</td>
<td>Angiogenesis (integrin αβ3)</td>
<td>SPECT</td>
<td>Yes (10 patients)</td>
</tr>
<tr>
<td>MNP, 111indium-oxine</td>
<td>Stem cells</td>
<td>MRI, SPECT</td>
<td>Yes (in cancer, 11 patients49)</td>
</tr>
</tbody>
</table>

SMC indicates smooth muscle cell; EC, endothelial cell; and FDA, Food and Drug Administration.

*For a more complete list, please see References 8 and 11.
electric cardioversion for atrial fibrillation or before percutaneous mitral valvuloplasty.

Evaluation of Novel Pharmaceuticals in Clinical Trials
The decision to proceed from phase I/II to costly phase III clinical trials often is made without the knowledge of whether a new drug has achieved its intended molecular effect. To address this issue, there is substantial interest in evaluating biomarkers and surrogate end points as measures of drug efficacy in patients, with a major focus on serum biomarkers. However, although frequently readily accessible, serum biomarkers often do not provide a readout of the action of a drug in the targeted diseased tissue. In contrast, imaging of inflammation (eg, via magnetic nanoparticle-enhanced MRI, [18F]-fluorodeoxyglucose [18FDG] PET imaging, or catheter-based protease NIRF imaging), for example, could provide a direct in vivo readout of novel antiinflammatory pharmaceuticals targeted to atherosclerosis. Such measures also could complement methods that measure changes in atheroma volume such as multicontrast MRI or intravascular ultrasound. Consequently, new pharmaceuticals with positive phase I/II molecular imaging substudies might be ideal candidates to proceed to phase III studies in a cost-effective fashion.

Molecular Imaging in Cardiovascular Medicine: Clinical Applications
Atherosclerosis
Unheralded rupture of high-risk atherosclerotic plaques causes many myocardial infarctions and sudden cardiac deaths. Current imaging methodologies that typically image plaque anatomy do not identify such high-risk lesions. Identification of these lesions in relevant vascular beds (coronary and carotid arteries) could alter systemic therapies (ie, prescribing higher statin doses or adjunctive treatments despite “target” serum lipid levels) and possibly guide local therapies (eg, intracoronary stenting of high-risk lesions) in patients at very high risk. To meet this need, many molecular imaging studies of atherosclerosis target inflammation, a critical process underlying the progression and rupture of atherosclerotic lesions. A number of imaging agents are emerging for atherosclerosis detection (reviewed elsewhere); here, we present leading candidates that could affect clinical practice considerably.

Imaging of Macrophages
Macrophages, key effector inflammatory cells in atherosclerosis, abound in coronary plaques that have caused sudden cardiac death. Imaging of macrophages is an appealing approach to detect inflammation in plaques prone to clinical complications. Two clinical strategies have recently demonstrated success in this area: nanoparticle-enhanced MRI and 18FDG PET imaging.

Clinical dextran-coated magnetic nanoparticles (MNPs) consist of a 3-nm superparamagnetic iron oxide core that induces strong MRI contrast (signal reductions) on T2- and T2*-weighted images. Clinical application of this compound has flourished in the detection of cancer metastases.

Recent investigations establish that MNPs can noninvasively image macrophages in carotid atheromata, with validation in carotid endarterectomy specimens (Figure 1). MNP-enhanced MRI is now being explored as a surrogate end point in a randomized clinical trial of high-dose versus low-dose statin therapy, with the hypothesis that higher statin doses will better suppress macrophage accumulation in carotid atheromata. Challenges of this approach stem from the intrinsic lower sensitivity of MRI compared with other imaging platforms, limiting the signal-to-noise ratio in high-resolution images required for coronary or carotid plaques. A potential gain in MNP imaging in the coronary arteries might be realized with intravascular MRI catheters. In addition, new positive contrast sequences may augment the detection of MNPs in vivo. In the future, multimodality imaging nanoparticles for MRI and optical imaging or novel MNPs that target vascular cell adhesion molecule should expand the utility of MNPs in the clinic (Figure 2).

18FDG is a glucose analog and positron emitter (half-life, 110 minutes) that concentrates in metabolically active cells after glucose transport and hexokinase-mediated phosphorylation. Several recent studies demonstrate that this agent accumulates in carotid atheroma and that its uptake correlates with macrophages as opposed to smooth muscle cells. A recent gain has been in the integration of PET with high-resolution CT and/or MRI to allow reliable coregistration of molecular and anatomic information (Figure 3). With the development of a radiopharmaceutical network spurred by the growth of cancer imaging studies, PET imaging
studies of vascular inflammation should expand considerably in the next several years, because centers will not require on-site cyclotrons. Similar to dextran-coated MNPs, several clinical trials are using $^{18}$FDG PET to quantify reductions in carotid plaque inflammation after statin pharmacotherapy. Challenges of PET imaging include the need for ionizing radiation, a considerable limitation to screening low-risk subjects. Furthermore, the radiation exposure will increase if coronary or carotid CT angiography is performed concomitantly for anatomic coregistration. In addition, $^{18}$FDG PET detection of macrophage-rich coronary plaques may suffer from substantial background uptake by metabolically active myocardium. Potential methods to improve the utility of coronary plaque $^{18}$FDG PET imaging include suppression of myocardial $^{18}$FDG signal by high-fat/low-glucose diets or $\beta$-adrenergic blocker before imaging, ECG and respiratory gating, or possibly the use of intravascular radiation detectors that may preferentially detect radioisotopes physically near the catheter. In addition, newer macrophage-specific targeted PET agents may overcome the limitation of background signal from metabolically active myocardium.

Finally, 2 very recent developments in the imaging of macrophages in atherosclerosis also deserve comment. First, a new study demonstrates the ability to target plaque macrophages with gadolinium-loaded immunomicelles targeted to the macrophage scavenger receptor. This agent may offer another MRI-based approach to image plaque macrophages. Second, a recent abstract demonstrates the ability to image macrophages with an iodine-loaded micelle (N1177) for CT. This approach may be particularly useful because CT angiography is emerging as a powerful method to image coronary arteries. This agent could thus provide enhancement...
of macrophage-rich coronary atheroma during coronary CT angiography.

**Imaging of Annexin V**
Annexin V is a 36-kDa protein that binds to phosphatidylserine, a molecule exposed on the membranes of dying cells, and may identify a subset of plaques with high rates of apoptosis potentially at greater risk for future complications.63,64 In a preliminary study of 4 patients, 99mTc-radiolabeled annexin V (or annexin A5) preferentially localized in patients with recent rather than remote transient ischemic attacks and was associated with macrophage and annexin V staining on plaque sections.39 However, annexin V in atheroma may target not only apoptotic cells in atheromata, with recent work showing colocalization of annexin V with nonapoptotic macrophages and with intraplaque hemorrhage.40 As with PET, SPECT imaging requires ionizing radiation, a drawback particularly when applied to the screening of low-risk individuals. Additional gains in annexin V–based imaging may occur with new targeted radioisotopes for PET imaging81 or magnetic nanoparticles for MRI.82

**Imaging of Protease Activity**
Augmented matrix metalloproteinase and cysteine protease expression occurs in the plaques of patients with atherosclerotic vascular disease.64 Because of their matrix-degrading properties, proteases likely mediate plaque remodeling and rupture and thus delineate plaques prone to complications. Recent experiments have imaged augmented cysteine and matrix metalloproteinase activity in atherosclerotic mice using near-infrared fluorescence imaging reporters.14,17,18 The strategy uses imaging agents that are quenched (silent) at baseline and then become strongly fluorescent after protease cleavage, producing a high signal-to-noise ratio in vivo (Figure 4). This strategy offers a new translational approach to image inflammation in atheroma.8,11 Because NIRF imaging is suitable for clinical cardiovascular imaging,8,11 we have recently constructed an NIRF catheter for intravascular imaging of protease activity.51 The catheter is a clinical-type guidewire that can be delivered percutaneously into coronary-sized vessels. In a recent experiment in atherosclerotic rabbits, a protease-activatable agent (Prosense750, VisEnMedical, Woburn, Mass) was administered intravenously, and the iliac vessels were imaged 24 hours later. Pullback of the intravascular NIRF catheter through blood, without the need for flushing, revealed strong focal NIRF signal in iliac plaques that was confirmed on ex vivo imaging (Figure 4).42 This approach may provide a high-resolution approach to image inflammation in coronary plaques and may identify high-risk lesions. Challenges of this approach include the limitations of photon attenuation and scattering with increasing depths and the semiquantitative and surface-weighted reflectance imaging, which may be addressable through the use of algorithms that correct for source-to-target variations in distance. In addition, the agent needs to undergo human testing in phase I clinical trials, currently planned for 2008.

**Imaging of Angiogenesis**
Microvessels within evolving plaques may cause intraplaque hemorrhage and thus identify high-risk atherosclerotic lesions.63,64 In particular, integrin αvβ3 is a key mediator of angiogenesis and thus may represent an important diagnostic and therapeutic target for diseases characterized by neovascularization.85 Recent experimental studies have used a gadolinium-coated perfluorocarbon nanomaterial (containing 90 000 gadolinium chelates) derivatized with an arginine-
glycine-aspartic acid peptidomimetic to target $\alpha_\beta$. Noninvasive MRI of experimental atherosclerotic plaques showed the ability of the agent to image angiogenesis in aortic plaques with 20% to 30% signal increases over untargeted perfluorocarbon agents.\textsuperscript{43} Very recent work has harnessed this nanoplatform to incorporate an antiangiogenic agent, fumagillin, to allow serial noninvasive MRI of antiangiogenic drug delivery and therapy.\textsuperscript{44} As with other MRI imaging agents, the application to coronary lesions will likely require advances in MRI detection systems.\textsuperscript{70,71}

**Thrombosis**
Thrombosis is the hallmark of multiple cardiovascular diseases, including acute coronary syndromes, stroke, and pulmonary embolism. However, despite the availability of useful diagnostic methods for thrombosis, several important issues remain unresolved. For example, practitioners would welcome noninvasive options over invasive, standard tests such as invasive coronary angiography or transesophageal echocardiography. Can we a priori identify fibrinolytically responsive thrombi to maximize the benefit (reperfusion) -to-risk (intracerebral bleeding) ratio, perhaps by imaging biologically acute thrombi via thrombin activity,\textsuperscript{15,86} activated factor XIII activity,\textsuperscript{87} or fibrin burden?\textsuperscript{72} Two recent advances in thrombosis reporter imaging agents for clinical use are highlighted next.

**Imaging of Fibrin**
Thrombin-mediated cleavage of fibrinogen yields fibrin monomers, which then polymerize and undergo cross-linking to form a stable clot. Both arterial and venous thrombi contain fibrin, making fibrin an appealing target for thrombosis imaging. Investigated as a scintigraphic imaging target almost 2 decades ago,\textsuperscript{88} a recent advance has been the development of a small-molecule fibrin-targeted agent for MRI (EP-2104R, Epix Pharmaceuticals, Lexington, Mass).\textsuperscript{23,60,89–92}

With a 10-fold improvement in spatial resolution over nuclear approaches, MRI is better suited to image smaller vessels such as the carotid and coronary arteries. Although cardiovascular MRI has well-appreciated advantages,\textsuperscript{9} the lower inherent sensitivity of MRI challenges the construction of molecular MRI agents. To overcome this limitation, the fibrin-targeted MRI agent capitalizes on 3 amplification strategies. First, the agent is based on a peptide, enabling faster binding kinetics compared with large-molecule (antibody) approaches, a key consideration in thrombosis detection. Second, the peptide was derived from phage-display screening technology and was selected to bind fibrin but not its precursor, fibrinogen; this property minimizes background signal from circulating fibrinogen, permitting faster detection of the enhanced thrombus. Third, the agent incorporates multivalency, with 4 gadolinium molecules conjugated to each peptide ligand, further increasing the thrombus target-to-background ratio. Extensive preclinical work has demonstrated considerable MRI enhancement of pulmonary embolism, atrial thrombi, and coronary stent thrombosis.\textsuperscript{23,60,89–91}

In addition, a rigorous experimental study demonstrated that fibrin is a stable imaging target in various ages of thrombi (<6 hours to 1 month old),\textsuperscript{92} a feature that should further improve its sensitivity for clinical thrombosis detection.

The agent is now under investigation in phase II clinical trials in a range of thrombosis syndromes.\textsuperscript{47} In a preliminary study of 52 patients imaged 2 to 24 hours after injection of the agent, there was substantial enhancement of atrial and ventricular thrombi, deep venous thrombosis, and carotid arterial thrombi (Figure 5). Several intriguing applications of high-resolution fibrin imaging include the detection of left atrial thrombi, offering a potential noninvasive option to transesophageal echocardiography, as discussed earlier. In addition, the agent improved the detection of recurrent deep venous thrombosis, a vexing problem for anatomic or flow-based diagnostic imaging methods. Further studies will determine whether the agent will permit rapid detection of thrombosis (<1 hour after injection) in more urgent situations such as acute coronary syndromes or pulmonary embolism. Finally, a recent development in fibrin imaging is the development of fibrin-targeted nanoparticles for CT molecular imaging of thrombus.\textsuperscript{93} Further in vivo investigation with this agent could augment the ability of CT to diagnose pulmonary embolism, stroke, or acute coronary syndromes.

**Imaging of Platelets**
Platelets are a major focus for modern antithrombotic therapies, and an important molecular target is the fibrin receptor integrin $\alpha_\text{IIb}\beta_3$ (glycoprotein IIb/IIIa), a 228 kDa heterodimeric protein that mediates platelet aggregation and promotes thrombus propagation.\textsuperscript{94} A US Food and Drug Administration–approved agent for SPECT imaging of platelet glycoprotein IIb/IIIa is $\text{Tc}^{99m}$-apcitide (Berlex Laborato-
ries, Wayne, NJ), an arginine-glycine-aspartic analog that competes with fibrinogen for binding to platelet glycoprotein IIb/IIIa. In a clinical trial of 78 patients, $^{99m}$Tc-apcitide SPECT imaging proved sensitive (92%) and specific (82% to 90%) for both a first deep venous thrombosis and a recurrent deep venous thrombosis.\textsuperscript{45} As with EP-2104R, specific diagnosis of thrombosis may represent an advantage over traditional diagnostic methods, as was highlighted in a case report of a patient with recurrent pulmonary embolism.\textsuperscript{46} Unexplored applications include the ability to image glycoprotein IIb/IIIa in coronary arterial thrombi to diagnose acute coronary syndromes and to guide and assess the effect of glycoprotein IIb/IIIa antagonists or other upstream platelet inhibitors. Because of the relatively low resolution of SPECT, such a study would likely require coronary CT angiography to visualize and anatomically coregister the coronary artery.

**Myocardial Infarction**

After myocardial infarction, a subset of patients may develop mechanical complications or ventricular dilatation and progression to heart failure. Identification of these at-risk patients has great potential to guide targeted clinical evaluation and pharmacological therapies. Accordingly, a number of preclinical imaging strategies have evolved for the detection of postinfarction matrix metalloproteinase activity, angiogenesis, activated factor XIIIa, apoptosis, macrophages, and stem cell delivery and thus offer new approaches to stratify subjects with myocardial infarction. Two recent developments in the clinical application of these approaches are discussed next.

**Imaging of Angiogenesis**

Angiogenesis, the growth of new blood vessels, modulates post–myocardial infarction healing and subsequent ventricular remodeling.\textsuperscript{55,90} A preliminary SPECT study of 10 acute myocardial infarction patients used an integrin $\alpha_{\text{v}}\beta_{3}$-targeted agent ($^{99m}$Tc-NC100692, GE Healthcare, Oslo, Norway) to assess cardiac angiogenesis.\textsuperscript{49} After percutaneous coronary revascularization, patients underwent perfusion imaging with $^{99m}$Tc-MIBI SPECT and echocardiography to assess the size of the infarct. Three weeks after myocardial infarction, $^{99m}$Tc-NC100692 SPECT imaging was performed to image infarct angiogenesis. Focal signal colocalized in the infarct zone, indicating angiogenesis in the healing infarct (Figure 6). Further analysis will reveal whether the extent of angiogenesis correlates with adverse ventricular remodeling and clinical outcome. This platform also may ultimately allow assessment of angiogenic therapies in post–myocardial infarction patients.\textsuperscript{49} The results suggest that an analogous scheme could label cardiac-targeted stem cells before delivery to post–myocardial infarction patients. Given the high-resolution imaging capabilities of cardiac MRI, MNP labeling in particular could shed light on the fate of stem cells in the hearts of living subjects. Challenges of the approach include the potential loss of the MNPs or the $^{111}$indium-oxine label with stem cell division and the possible transfer of the agents to nonstem cells such as macrophages.\textsuperscript{99}

**Outlook**

Treatment of patients with cardiovascular disease increasingly incorporates molecular and cellular markers of disease into management algorithms. Molecular imaging will offer the ability to provide biological detail in patients and, although still in its infancy, shows promise for imaging of atherosclerosis, thrombosis, and myocardial infarction. Further growth in reporter imaging agents possessing nanotechnological amplification schemes and expansion of high-resolution imaging systems for nuclear/CT, MRI, and optical imaging should enable molecular imaging to become an integral component of personalized medicine.

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