In Vivo Tracking of Stem Cells for Clinical Trials in Cardiovascular Disease

John V. Frangioni, MD, PhD; Roger J. Hajjar, MD

Abstract—Various stem cells hold promise for the treatment of human cardiovascular disease. Regardless of stem cell origin, future clinical trials will require that the location and number of such cells be tracked in vivo, over long periods of time. The problem of tracking small numbers of cells in the body is a difficult one, and an optimal solution does not yet exist. We review the many contrast agents and detectors that have been proposed for stem cell tracking during clinical trials, define the characteristics of an ideal imaging technology, and suggest future directions for research. (Circulation. 2004;110:3378-3384.)

Key Words: stem cells  imaging  trials  radiology

With the rapid increase of reported cases of stem cells being used to treat cardiovascular disease, it has become apparent that an urgent need exists to track stem cells in vivo during clinical trials.

For example, stem cell therapy for heart failure addresses an important problem in clinical medicine. Heart failure is a major cause of morbidity and mortality in the United States. The rates of new and recurrent heart failure events increase substantially with age. In patients aged 65 and older, congestive heart failure is the single most frequent cause of hospitalization in the United States. Despite substantial advances in the clinical management of heart failure, the diagnosis continues to carry a grave prognosis with an overall 5-year mortality rate of ≈50%. This rate is substantially worse in more severely affected patient subsets. An understanding of the role of stem cells in repopulating damaged areas in the heart would help target these diseased areas.¹

The problem of imaging small numbers of cells in the living subject is not limited to stem cell–based treatments in cardiology but has broad applicability in oncology, immunology, and transplantation.

Ideal Imaging Technology for Stem Cell Tracking

Successful in vivo imaging requires that a contrast agent associated with a stem cell exert an “effect size” sufficient for detection by imaging hardware. Although the most attractive contrast agents for tracking are endogenous ones (ie, normal components of the stem cell), their effect size is extremely small. This review will focus on exogenous contrast agents, which have a large and controllable effect size. It also will focus on imaging technology that has clinical relevance because many preclinical small animal studies in the field of stem cell tracking are not translatable to clinical practice.

The 8 characteristics of an ideal imaging technology for stem cell tracking are presented in Table 1. First, and foremost, the exogenous contrast agent must be biocompatible, safe, and nontoxic. This is especially important when nanotechnology solutions to the tracking problem (mentioned below) are considered, because most solid-state devices will be composed of materials that do not have proven long-term safety in vivo.

Another consideration is the need for genetic modification of the stem cell or perturbation of its genetic program by the contrast agent itself. Several imaging techniques, such as enzymatic conversion of an injected substrate and receptor-based binding, require stable integration of transgenes. This strategy may be combined with genetic manipulation of stem cell populations to enhance the viability, differentiation, and coupling of these cells with the myocardium. These types of manipulations add significant cost, regulatory roadblocks, and the potential to induce genetic abnormalities, including uncontrolled growth and malignancy.² Although exogenous genes have the distinct advantage of not being diluted by cell division and have the potential to induce cell survival or suicide on demand,³ it is unclear at present if the extra step of genetic manipulation will become routine in human clinical stem cell trials.

Ideally, imaging technology used for stem cell tracking would have single-cell sensitivity and would permit quantification of exact cell numbers at any anatomic location. Single-cell sensitivity is especially important in a new field such as that of stem cells because the pattern of migration of stem cells, even after local injection, is unknown, and there is
Luciferase to detect cells in vivo. Four published studies, 3 in genes and substrates described to date generate only visible (400 to 700 nm) light, which has very high absorption and scatter in living tissue. This precludes use of the technique in animals larger than rats, and even in mice false-negative scanning can occur, dependent on cell depth. Bioluminescence also requires the stable expression of nonhuman genes, and the injection of high concentrations of potentially immunogenic, nonhuman substrates, such as luciferin and coelenterazine. It is therefore unlikely that this technique will be used clinically.

Fluorescence imaging utilizes organic (eg, green fluorescent protein, small-molecule polymethines) or organic/inorganic hybrids (eg, quantum dots) as exogenous contrast agents for in vivo imaging (reviewed in Frangioni95). Because of high photon absorption and scatter at visible wavelengths, only near-infrared (NIR) (700 to 1000 nm) fluorophores have clinical potential. The major problem with NIR fluorescence is that even with tomographic imaging methods, detection is limited to only 4 to 10 cm of tissue (reviewed in Ntziachristos et al10 and Sevick-Muraca et al11). Hence, clinical use of NIR fluorescence likely will be limited to near-surface applications, such as intraoperative imaging.12–14 A major advantage of NIR fluorescence is its compatibility with conventional microscopy,15,16 permitting single-cell detection of stem cells in pathological specimens. Ex vivo histological detection of stem cells undoubtedly will be required in clinical trials. Major disadvantages of NIR fluorescence are the dilution of the agent with each cell division and the possibility of uptake by nonstem cells after stem cell death.

**Detection Methods for In Vivo Stem Cell Tracking**

At present, no imaging technology fulfills the 8 criteria presented above, although some come close. The following is a discussion of the advantages and disadvantages of various imaging modalities that might be considered for clinical stem cell trials (Table 2).

**X-Ray–Based Methods**

Plain films and computed tomography (CT) are the most readily available clinical imaging modalities. Unfortunately, contrast generation requires extremely high concentrations of high-density/high–atomic number materials such as iodine, gadolinium, or metals. To render a stem cell or collection of stem cells visible by using even a solid metal, the volume of metal associated with the cell volume must be equal to or greater than the inverse of its density. For example, it would take approximately one eighth of the cell volume in solid iron to generate a signal above background during CT scanning. Such contrast is difficult to achieve, rendering x-ray–based methods unlikely to play a direct role in stem cell tracking at the present time.

**Optical Imaging**

Two complementary optical imaging methods, bioluminescence and fluorescence, can be used for stem cell tracking. Bioluminescence utilizes light generated by the enzyme luciferase to detect cells in vivo. Four published studies, 3 in mice4–6 and 1 in rats,7 utilized bioluminescence to track the distribution and engraftment of stem cells in vivo. Unfortunately, luciferase genes and substrates described to date generate only visible (400 to 700 nm) light, which has very high absorption and scatter in living tissue. This precludes use of the technique in animals larger than rats, and even in mice false-negative scanning can occur, dependent on cell depth.8 Bioluminescence also requires the stable expression of nonhuman genes, and the injection of high concentrations of potentially immunogenic, nonhuman substrates, such as luciferin and coelenterazine. It is therefore unlikely that this technique will be used clinically.

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**Ultrasound**

Because cardiologists likely will conduct the majority of clinical studies of stem cells in cardiovascular applications, tracking by echocardiography would be extremely convenient. Contrast for echocardiography is generated by acoustic interfaces such as water/gas (eg, microbubbles, perfluorocarbons). Although a single unit of contrast is on the order of 0.25 to 1 μm in diameter, the generated acoustic perturbation appears much larger. Echocardiography therefore has the potential to detect a single cell loaded with a single unit of contrast.17 Nevertheless, methods to accumulate contrast intracellularly are not yet robust, and effects on cell motility, etc, are not known. An additional problem is that echogenic contrast agents cast an acoustic “shadow” below the first unit of contrast detected, thus precluding accurate quantification of cell number. Such contrast agents are subject to dilution during cell division and transfer to nonstem cells after cell death. Finally, spatial resolution of ultrasound is limited, and many anatomic sites are inaccessible.

**Single-Photon Emission Computed Tomography**

High-energy gamma rays emitted by radioactive atoms as 99mTc, 111In, and 123I are detected by rotating a collimated gamma camera around the subject and reconstructing a 3-dimensional image. Three strategies for in vivo stem cell detection have been described: direct loading with a radionuclide,18–21 enzymatic conversion and retention of a radioactive...
TABLE 2. Contrast Agents and Detectors for In Vivo Stem Cell Tracking

<table>
<thead>
<tr>
<th>Modality</th>
<th>Contrast Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain films</td>
<td>High-density/high-atomic number materials (eg, iodine, gadolinium)</td>
<td>Inexpensive, fast, readily available, few clinical contraindications</td>
<td>Requires molar concentrations of contrast agent, 2D projections only, quantification difficult, ionizing radiation</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>High-density/high-atomic number materials (eg, iodine, gadolinium)</td>
<td>Readily available, 3D, full-body scanning</td>
<td>Requires molar concentrations of contrast agent, artifacts from bone and cardiac devices, ionizing radiation</td>
</tr>
<tr>
<td>Optical: bioluminescence</td>
<td>Luciferase substrates</td>
<td>Sensitive, no ionizing radiation</td>
<td>Requires genetic modification of stem cell and intravenous injection of contrast agent, limited to small animal use</td>
</tr>
<tr>
<td>Optical: fluorescence</td>
<td>Near-infrared fluorophores</td>
<td>Sensitive, no ionizing radiation, fast, ex vivo single-cell histological detection</td>
<td>Limited to small animal or intraoperative use, dilution of contrast agent with cell division, potential transfer of contrast agent to nonstem cells</td>
</tr>
<tr>
<td>Ultrasound/echocardiography</td>
<td>Microbubbles of various materials</td>
<td>Readily available, fast, no ionizing radiation, potential in vivo single-cell detection</td>
<td>Limited anatomic access, relatively low resolution, quantification difficult, dilution of contrast agent with cell division, potential transfer to nonstem cells</td>
</tr>
<tr>
<td>SPECT</td>
<td>High-energy gamma emitters (eg, $^{99m}$Tc, $^{111}$In)</td>
<td>Sensitive, 3D full-body scanning, no dilution of effect size with cell division (transgenic approaches)</td>
<td>Requires genetic modification of stem cell and/or intravenous injection of contrast agent, ionizing radiation, quantification can be difficult</td>
</tr>
<tr>
<td>PET</td>
<td>High-energy positron emitters (eg, $^{18}$F, $^{124}$I)</td>
<td>Sensitive, 3D full-body scanning, no dilution of effect size with cell division (transgenic approaches), quantification possible but can be difficult</td>
<td>Requires genetic modification of stem cell and/or intravenous injection of contrast agent, ionizing radiation, not readily available</td>
</tr>
<tr>
<td>MRI</td>
<td>Lanthanides (eg, gadolinium), superparamagnetic iron-oxide nanoparticles (eg, MIONs)</td>
<td>3D full-body scanning, no ionizing radiation, quantification possible but can be difficult</td>
<td>Contraindicated with many cardiac devices, some contrast agents are insensitive, dilution of contrast agent with cell division, potential transfer to nonstem cells</td>
</tr>
<tr>
<td>MRI/fluorescence</td>
<td>Fluorophore-labeled T1 or T2/T2* agents</td>
<td>Intraoperative image-guided delivery of stem cells, 3D full-body scanning, no ionizing radiation, quantification possible but can be difficult, ex vivo single-cell detection</td>
<td>Contraindicated with many cardiac devices, some contrast agents are insensitive, dilution of contrast agents with cell division, potential transfer to nonstem cells</td>
</tr>
<tr>
<td>MRI/fluorescence/ultrasound</td>
<td>Fluorophore, perfluorocarbon, and Gd$^{3+}$-labeled liposomes</td>
<td>Intraoperative image-guided delivery of stem cells, 3D full-body scanning, no ionizing radiation, quantification possible but can be difficult, potential in vivo and ex vivo single-cell detection</td>
<td>Contraindicated with many cardiac devices, dilution of contrast agents with cell division, potential transfer to nonstem cells, unknown effects on cellular physiology</td>
</tr>
</tbody>
</table>

substrate (reviewed in Gambhir et al\textsuperscript{22}), and receptor-mediated binding.\textsuperscript{22,23} Direct loading is problematic given the tradeoff between half-life and long-term exposure to ionizing radiation and given the possibility of transfer of the radiometal from stem cells to nonstem cells.

Enzymatic conversion/retention has been used for both single-photon emission CT (SPECT) and positron emission tomography (PET) (see below) substrates. The significant advantages of this strategy include the ability to follow stem cells indefinitely after stable integration of the transgene, the absence of marker dilution by cell division, and the ability to destroy stem cells by administration of a suicide drug specific for the enzyme. The disadvantages of this strategy include the need to genetically manipulate the stem cell ex vivo and the need to administer a substrate intravenously for each imaging session.

Receptor-mediated targeting requires stable expression of a receptor not found elsewhere in the body and intravenous injection of a radioactive receptor ligand.

Positron Emission Tomography

PET utilizes coincident detection of 2 anti-parallel 511-keV gamma rays emitted after positron annihilation. Tradeoffs exist between the higher energy of the photons, coincident detection, and detector efficiency, but overall, PET has a higher sensitivity than SPECT and permits more accurate quantification of cell number. Although the 3 strategies mentioned above for SPECT can be used for stem cell tracking with PET, the most advanced by far is the stable integration of a mutant herpes simplex type 1 thymidine kinase (TK) into stem cells and periodic intravenous injection of the TK substrate $^{18}$FHBG.\textsuperscript{7} Although it permits tracking and quantification of stem cells over the course of months, this strategy requires genetic manipulation of the stem
cells, an infrastructure for $^{18}$F chemistry, a PET scanner, and radiation exposure (albeit it intermittent) to the stem cells and subject.

Additional caveats for SPECT- and PET-based tracking of stem cells include nonspecific uptake of the radiotracer by normal tissue, relatively low efficiency of collimated SPECT cameras, and photon attenuation by tissue. Although tissue photon attenuation can be corrected in some cases, for example by employing hybrid nuclear medicine/CT systems, it reduces sensitivity, and prevents accurate quantification of stem cell number.19 Whether used for attenuation correction or not, hybrid CT systems have the major advantage that they permit coregistration of anatomic (CT) and physiological (SPECT or PET) images.

Another (often overlooked) issue is the inherent limits of radioactive methods for stem cell detection. A typical patient dose of 10 to 20 mCi is equivalent to only 3.5 to $7 \times 10^{12}$ radioactive molecules of contrast agent. In typical clinical nuclear medicine imaging, $\approx 10^9$ radioactive molecules per milliliter (a milliliter being the order of magnitude of clinical resolution) are required to generate detectable signal above background (J. Anthony Parker, MD, PhD, Associate Professor of Radiology, Beth Israel Deaconess Medical Center and Harvard Medical School, personal communication, April 15, 2004). To detect a single stem cell, $\approx 0.01\%$ of the injected dose would have to be concentrated in/on the cell, which is a formidable technical challenge.

**Magnetic Resonance Imaging**

Given its extraordinary 3-dimensional capabilities and high safety profile, magnetic resonance imaging (MRI) is the imaging modality used by most research studies to track stem cells in vivo. At this point in time, MRI imaging techniques can be divided into those generating primarily T1 contrast and those generating primarily T2/T2* contrast.

T1 contrast agents are those that utilize the lanthanide gadolinium (Gd$^{3+}$), which changes the relaxivity of protons from associated water molecules and increases the signal on T1-weighted images. Unfortunately, with presently available field strengths, Gd$^{3+}$-based contrast requires 50- to 500-µmol/L concentrations of low-molecular-weight Gd$^{3+}$-containing molecules or attachment to bulky scaffolds such as dendrimers and dextrans to increase the T1 effect. At least 3 studies in the literature demonstrate convincingly, however, that Gd$^{15}$-containing scaffolds, loaded via pino/endocytosis into stem cells, permit tracking for up to 6 weeks.24–26

T2/T2* contrast is by far the most widely used technique for stem cell imaging studies using MRI. This is a consequence of the observation made by the Weissleder group in the early 1990s that superparamagnetic iron oxide nanoparticles (also known as monocrystalline iron oxide nanocrystals [MIONs], ultrasmall superparamagnetic iron oxide [USPIOs]) congeal in endosomes after endocytosis, resulting in magnification of their susceptibility effects. More recent formulations of their susceptibility effects. More recent formulations containing molecules or attachment to bulky scaffolds such as dendrimers and dextrans to increase the T1 effect. At least 3 studies in the literature demonstrate convincingly, however, that Gd$^{15}$-containing scaffolds, loaded via pino/endocytosis into stem cells, permit tracking for up to 6 weeks.24–26

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Published Stem Cell Imaging Studies

Tracking the movement of different types of stem cells has been an important focus in studies of cellular cardiomyoplasty (Table 3). The different types of stem cells have specific characteristics in their mode of delivery and engraftment.38–45 Mesenchymal stem cells (MSCs), which can be isolated in adults and expanded in culture, have phenotypic characteristics of smooth muscle, skeletal myoblasts, and cardiac myocyte cells. A number of studies have shown that MSCs can reverse adverse remodeling when injected directly into the infarcted heart or after homing to the infarcted area when injected intravenously. Studies with MSCs have been performed in rodents and larger animals, and the fate and movements of the MSCs have been imaged with MRI, radioscintigraphy, and visible fluorescence. Hematopoietic cells and endothelial cells also have been targeted toward areas of infarcts within the heart and also have been visualized by various imaging modalities. With these cells, the therapeutic end point also includes neovascularization and angiogenesis, which often require other imaging modalities such as intravitreal microscopy and optical coherence tomography for assessment. Finally, embryonic stem cells are being tested in cardiac repair, and because their potential to differentiate and transmigrate is greater than that of adult stem...
cells, multiple imaging modalities may be required to assess the overall distribution of these cells.

**Future Directions**

Given the inherent limitations of currently available imaging technology, future research should focus on improving sensitivity while minimizing patient exclusion, study cost, and study complexity. Novel ideas would be welcomed in the field. Paramagnetic chemical exchange saturation transfer (PARACEST) agents for MRI have the potential to improve MRI sensitivity by up to 2 orders of magnitude (reviewed in Zhang et al.46). Terahertz47 and other electromagnetic frequencies offer certain advantages, although exogenous contrast agents do not yet exist. Solid-state nanotechnology solutions, however remote at present, are particularly attractive because they could potentially provide noninvasive, real-time monitoring of intracellular pH, calcium, etc, as well as anatomic location, of single stem cells.

**Conclusion**

In conclusion, x-ray techniques do not provide adequate contrast sensitivity for cardiovascular stem cell tracking in the clinical setting. Bioluminescence is limited to small animal studies and NIR fluorescence to near-surface and histological applications. Ultrasound/echocardiography has the potential for single-cell detection but has limited anatomic accessibility, resolution, and quantification. High-energy photon imaging (SPECT or PET) has high sensitivity, but for long-term tracking it requires genetic manipulation of the stem cell, stable expression of a transgene, and multiple exposures to ionizing radiation. MRI provides excellent 3-dimensional anatomy but is contraindicated for many patients and has limited availability at many institutions, and some contrast techniques have low sensitivity. Although multimodality contrast agents might improve the prospects for stem cell tracking both in vivo and ex vivo, no currently available imaging technology is ideal. Impending clinical trials utilizing stem cells must define, carefully, the limits of the imaging technology chosen.

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**References**


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**TABLE 3. In Vivo Tracking Studies for Various Stem Cell Types**

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<thead>
<tr>
<th>Stem Cell Type/Host Species</th>
<th>Imaging Modality</th>
<th>Contrast Agent(s)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenchymal stem/progenitor cell</td>
<td>Whole-body visible fluorescence</td>
<td>Enhanced green fluorescent protein</td>
<td>45</td>
</tr>
<tr>
<td>Mice</td>
<td>3D confocal laser scanning microscopy</td>
<td>Calcein</td>
<td>42</td>
</tr>
<tr>
<td>Rat</td>
<td>Planar radioscintigraphy</td>
<td>$^{111}\text{In}$ oxine</td>
<td>18</td>
</tr>
<tr>
<td>Rat</td>
<td>Planar radioscintigraphy/ex vivo visible fluorescence</td>
<td>$^{99m}\text{Tc}$-exametazime/PKH2</td>
<td>20</td>
</tr>
<tr>
<td>Rat</td>
<td>MRI/ex vivo visible fluorescence microscopy</td>
<td>Iron oxide nanoparticles/enhanced GFP</td>
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<tr>
<td>Rabbit</td>
<td>Radioscintigraphy</td>
<td>$^{125}\text{I}$- and $^{131}\text{I}$-transferin (human)</td>
<td>44</td>
</tr>
<tr>
<td>Pig</td>
<td>SPECT</td>
<td>$^{111}\text{In}$ oxine</td>
<td>19</td>
</tr>
<tr>
<td>Pig</td>
<td>MRI/ex vivo visible fluorescence microscopy</td>
<td>Fluorescein-labeled iron nanoparticles</td>
<td>36</td>
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<tr>
<td>Hematopoietic/endothelial progenitor cell</td>
<td>Bioluminescence</td>
<td>Luciferase/luciferin</td>
<td>4</td>
</tr>
<tr>
<td>Mouse</td>
<td>Intravital visible fluorescence microscopy</td>
<td>PKH26 and PKH67</td>
<td>39,40</td>
</tr>
<tr>
<td>Rat</td>
<td>Planar radioscintigraphy/ex vivo visible fluorescence</td>
<td>$^{111}\text{In}$ oxine/DILDL</td>
<td>21</td>
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<tr>
<td>Human</td>
<td>MRI</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>Radioscintigraphy (ex vivo)/visible fluorescence microscopy</td>
<td>PKH26 and $^{125}\text{I}$-PKH95</td>
<td>38</td>
</tr>
<tr>
<td>Dog</td>
<td>Whole-embryo visible fluorescence</td>
<td>Dil-conjugated acetylated LDL</td>
<td>41</td>
</tr>
<tr>
<td>Embryonic stem cells</td>
<td>MRI/ex vivo visible fluorescence microscopy</td>
<td>Iron oxide nanoparticles/enhanced GFP</td>
<td>43</td>
</tr>
</tbody>
</table>


19. Chin BB, Nakamoto Y, Bulte JW, et al. 111In oxine labelled mesen-


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