Coronary heart disease is usually a result of atherosclerotic progression, which is characterized by the narrowing of small blood vessels that supply blood and oxygen to the heart. Despite recent advances in pharmacotherapy and interventional procedures, coronary heart disease remains the leading cause of heart failure in the western world[1]. Owing to the limited regenerative capacity of cardiac cells and subsequent detrimental ventricular remodeling after myocardial infarction, heart transplantation is currently the only definitive treatment for end-stage cardiovascular disease. Yet, the lack of suitable organs and high cost limit the number of heart transplants that are performed. Stem and progenitor cells possess the capability of self-renewal and can differentiate into organ-specific cell types with the potential to reconstitute damaged organ systems. Thus, many types of stem cell therapeutics have emerged for cardiac repair with rapid translation to clinical trials, sometimes without extensive preclinical testing.

Preclinical cardiovascular stem cell studies in animal models of myocardial infarction have shown encouraging results ranging from restoration of ventricular function to improved myocardial perfusion[2]. The results from clinical trials, however, have been mixed (Table 1). The BOOST trial demonstrated the safety and feasibility of intracoronary infusion of autologous bone marrow cells and early improvements of left ventricular function[3], but the improvements were not sustained after 5 years[4]. In addition, other double-blinded, randomized and placebo-controlled trials showed little or no long-term benefits[5–7]. Each clinical trial has involved a relatively small number of patients with a primary end point of safety. However, meta-analyses of these trials have generally shown a slight positive trend towards improved cardiac function[8–12].

Noninvasive imaging, such as echocardiography, MRI, PET, SPECT and CT, can play a pivotal role in tracking stem cell engraftment and expand these imaging modalities beyond merely assessing cardiac function. This article will provide an overview of the fundamentals of stem cell labeling techniques and discuss the advantages and disadvantages of each imaging modality with a focus on those with the greatest potential for clinical translation.

### Stem cell labeling

Embryonic stem cells (ESCs), adult stem cells and induced pluripotent stem cells are the three major types of stem/progenitor cells that possess the ability to provide the building blocks for cardiovascular system repair. Owing to the ethical issues and the potential danger of teratoma formation of undifferentiated ESCs and the low reprogramming efficiency of induced pluripotent stem cells, adult stem cells (e.g., bone marrow-derived mesenchymal stem cells, skeletal myoblasts and cardiac/endothelial progenitor cells) have dominated current clinical investigations (Table 1).
Table 1. Clinical trials using stem cells for the treatment of cardiovascular disorders.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Conditions treated</th>
<th>n</th>
<th>Cell types</th>
<th>Delivery routes</th>
<th>Imaging modality</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOOST</td>
<td>AMI</td>
<td>60</td>
<td>Autologous BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[3,4,102–105]</td>
</tr>
<tr>
<td>COMPARE-AMI</td>
<td>AMI</td>
<td>14</td>
<td>CD133* enriched BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[106]</td>
</tr>
<tr>
<td>REPAIR-AMI</td>
<td>AMI</td>
<td>204</td>
<td>BM progenitors</td>
<td>Intracoronary</td>
<td>X</td>
<td>[107]</td>
</tr>
<tr>
<td>REGENT</td>
<td>AMI</td>
<td>200</td>
<td>Selected (CD34+CXCR4) BMC, unselected BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[108]</td>
</tr>
<tr>
<td>PROTECT-CAD</td>
<td>CAD</td>
<td>28</td>
<td>Autologous BMC</td>
<td>Endomyocardial</td>
<td>X</td>
<td>[109]</td>
</tr>
<tr>
<td>Chan et al.</td>
<td>(subgroup of PROTECT-CAD)</td>
<td>12</td>
<td>Autologous BMC</td>
<td>Endomyocardial</td>
<td>X</td>
<td>[110]</td>
</tr>
<tr>
<td>Brehm et al.</td>
<td>CMI</td>
<td>18</td>
<td>Autologous BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[111]</td>
</tr>
<tr>
<td>Fernandez-Aviles et al.</td>
<td>CMI</td>
<td>20</td>
<td>Autologous BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[112]</td>
</tr>
<tr>
<td>Fuchs et al.</td>
<td>CMI</td>
<td>10</td>
<td>Autologous BMC</td>
<td>Transendocardial</td>
<td>X</td>
<td>[113]</td>
</tr>
<tr>
<td>Galinanes et al.</td>
<td>Transmural MI</td>
<td>14</td>
<td>Autologous BMC</td>
<td>Transmyocardial</td>
<td>X</td>
<td>[114]</td>
</tr>
<tr>
<td>Hamano et al.</td>
<td>CMI</td>
<td>5</td>
<td>BMC</td>
<td>Transmyocardial</td>
<td>X</td>
<td>[115]</td>
</tr>
<tr>
<td>Strauer et al.</td>
<td>Heart failure</td>
<td>391</td>
<td>BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[116]</td>
</tr>
<tr>
<td>IACT</td>
<td>CAD</td>
<td>18</td>
<td>Autologous BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[117]</td>
</tr>
<tr>
<td>Janssens et al.</td>
<td>CMI</td>
<td>67</td>
<td>Autologous BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[6]</td>
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<tr>
<td>Kueth et al.</td>
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<td>5</td>
<td>BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[118]</td>
</tr>
<tr>
<td>Lunde et al.</td>
<td>STEMI</td>
<td>100</td>
<td>Mononuclear BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[119]</td>
</tr>
<tr>
<td>Perin et al.</td>
<td>CMI</td>
<td>21</td>
<td>Mononuclear BMC</td>
<td>Transendocardial</td>
<td>X</td>
<td>[120,121]</td>
</tr>
<tr>
<td>Silva et al.</td>
<td>Heart failure</td>
<td>5</td>
<td>Mononuclear BMC</td>
<td>Transendocardial</td>
<td>X</td>
<td>[122]</td>
</tr>
<tr>
<td>Arnold et al.</td>
<td>STEMI</td>
<td>37</td>
<td>Mononuclear BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[123]</td>
</tr>
<tr>
<td>van Ramshorst et al.</td>
<td>CMI</td>
<td>50</td>
<td>BMC</td>
<td>Transendocardial</td>
<td>X</td>
<td>[124]</td>
</tr>
<tr>
<td>Strauer et al.</td>
<td>AMI</td>
<td>20</td>
<td>Mononuclear BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[125]</td>
</tr>
<tr>
<td>FOCUS</td>
<td>CAD</td>
<td>87</td>
<td>Mononuclear BMC</td>
<td>Intramyocardial</td>
<td>X</td>
<td>[126]</td>
</tr>
<tr>
<td>Assmus et al.</td>
<td>CMI</td>
<td>75</td>
<td>CPC/BMC</td>
<td>Transcoronary</td>
<td>X</td>
<td>[127]</td>
</tr>
<tr>
<td>TOPCARE-AMI</td>
<td>AMI</td>
<td>20</td>
<td>CPC/BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[128–130]</td>
</tr>
<tr>
<td>Bartunek et al.</td>
<td>AMI</td>
<td>35</td>
<td>CD133* BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[131]</td>
</tr>
<tr>
<td>Goussetis et al.</td>
<td>CMI</td>
<td>8</td>
<td>CD133* BMC/CD133* CD34* BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[132]</td>
</tr>
<tr>
<td>Stamm et al.</td>
<td>AMI</td>
<td>12</td>
<td>CD133* BMC</td>
<td>Transendocardial</td>
<td>X</td>
<td>[133,134]</td>
</tr>
<tr>
<td>Losordo et al.</td>
<td>AMI</td>
<td>24</td>
<td>Autologous CD34*, G-CSF mobilized PBC</td>
<td>Transendocardial</td>
<td>X</td>
<td>[135]</td>
</tr>
<tr>
<td>TOPCARE-CHD</td>
<td>CMI</td>
<td>75</td>
<td>PBC, BMC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[127]</td>
</tr>
<tr>
<td>Choi et al.</td>
<td>AMI</td>
<td>73</td>
<td>G-CSF mobilized PBC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[136]</td>
</tr>
<tr>
<td>MAGIC Cell-DES</td>
<td>AMI</td>
<td>96</td>
<td>G-CSF mobilized PBC</td>
<td>Intracoronary</td>
<td>X</td>
<td>[137]</td>
</tr>
<tr>
<td>Chachques et al.</td>
<td>MI</td>
<td>20</td>
<td>Autologous skeletal myoblast</td>
<td>Intramyocardial</td>
<td>X</td>
<td>[138]</td>
</tr>
<tr>
<td>Dib et al.</td>
<td>MI</td>
<td>30</td>
<td>Autologous skeletal myoblast</td>
<td>Epicardial</td>
<td>X</td>
<td>[139]</td>
</tr>
</tbody>
</table>

AMI: Acute myocardial infarction; Angio: X-ray angiography; BMC: Bone marrow cell; CAD: Coronary arterial disease; CMI: Chronic myocardial infarction; CPC: Circulating blood-derived progenitor cell; Echo: Echocardiography; EPC: Endothelial progenitor cell; G-CSF: Granulocyte colony stimulating factor; MI: Myocardial infarction; MSC: Mesenchymal stem cell; PBC: Peripheral blood cell; STEM: ST-elevation myocardial infarction.
For noninvasive tracking of stem cells, the label should ideally be [13]:

- Inert and/or biocompatible
- Highly specific to target cells
- Detected at the level of a single or few cells

At present, there is no single label/probe that meets all these requirements in combination with a single imaging technique. However, each imaging modality has desirable characteristics that, in part, may drive the choice of stem cell labels (Table 2). In general, stem cell labeling falls into two primary methods: direct/physical labeling and indirect/genetic labeling.

Direct cell labeling typically requires incubation of a cell with the label of interest. The label may then be bound on the cell surface or internalized by the cell. As such, direct labeling is the simplest and most straightforward method that can be performed with a variety of probes to enable visualization of stem cells by noninvasive clinical imaging techniques [14]. For example, direct stem cell labeling using superparamagnetic iron oxide particles (SPIOs) and radioactive tracers (e.g., $^{111}$In and $^{18}$F) has been widely used for MRI [15-17] and radionuclide imaging [18,19], respectively. Optical imaging of stem cells labeled with fluorescence probes (e.g., near-infrared fluorophores and quantum dots) has been reported in animal models [20,21]. The primary disadvantages of direct labeling are label dilution/loss with cell division or cell death and inability to differentiate viable from dead cells due to retained label in situ or native cell uptake of label from dead cells. Thus, direct cell labeling is best for confirmation of cell delivery success and short-term localization of cells after delivery.

In contrast to direct stem cell labeling, genetic labeling of stem cells with reporter genes involves insertion of genetic material that encodes for an enzyme, receptor or protein that can then be imaged directly or interacts with a reporter probe to enable noninvasive visualization of the cell. Because only live cells can produce the reporter gene product, this technique is better at discriminating live from dead cells due to retained label in situ or native cell uptake of label from dead cells. Thus, direct cell labeling is best for confirmation of cell delivery success and short-term localization of cells after delivery.

In contrast to direct stem cell labeling, genetic labeling of stem cells with reporter genes involves insertion of genetic material that encodes for an enzyme, receptor or protein that can then be imaged directly or interacts with a reporter probe to enable noninvasive visualization of the cell. Because only live cells can produce the reporter gene product, this technique is better at discriminating live from dead cells due to retained label in situ or native cell uptake of label from dead cells. Thus, direct cell labeling is best for confirmation of cell delivery success and short-term localization of cells after delivery.
Echocardiography

Owing to its wide availability, low cost and lack of ionizing radiation, echocardiography is routinely used to assess cardiac function, diagnose pericardial disease and evaluate stem cell therapy efficacy. However, few studies have explored using echocardiography to track cells. In part, this is due to the low spatial resolution and lack

<table>
<thead>
<tr>
<th>Table 2. Advantages and disadvantages of labeling techniques by imaging modality.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modality</strong></td>
</tr>
<tr>
<td>US</td>
</tr>
<tr>
<td>MRI</td>
</tr>
<tr>
<td>SPECT/PET</td>
</tr>
<tr>
<td>SPECT</td>
</tr>
<tr>
<td>Optical Imaging</td>
</tr>
<tr>
<td>X-ray/CT</td>
</tr>
</tbody>
</table>

D2R: Dopamine type 2 receptor; Gd: Gadolinium; GFP: Green fluorescent protein; hNIS: Human NIS; HSV1-srtk: Herpes simplex virus-1 thymidine kinase (mutant form); US: Ultrasound.
of accuracy in cell quantification of ultrasound. Cardiac stem cell tracking using microbubbles [24,25] or CliniMACS® nanoparticles [26] have very recently been performed. In one study, the engraftment of genetically modified endothelial progenitor cells within a Matrigel™ plug was imaged with contrast-enhanced ultrasound using targeted microbubbles [25]. Two issues with microbubble technology are that the microbubble integrity cannot be maintained over time and the delivery of microbubbles outside the vascular space is challenging.

**MRI**

MRI is a multipurpose imaging modality that provides excellent soft tissue contrast with high spatial and moderate temporal resolution. Therefore, it has been frequently used in the clinic to assess cardiac anatomy, ventricular function, blood flow and myocardial perfusion. In noncardiac applications, MRI has been used to visualize individual labeled cells against a homogeneous background [27]. Stem cells can be directly labeled with a magnetic resonance (MR) contrast agent (e.g., gadolinium chelates and SPIOs) through endocytosis, magnetofection [28] or electroporation [29,30] approaches, or indirectly labeled with an MR reporter gene (e.g., ferritin) via viral [31] or nonviral transfection [32]. Thus, MRI offers the ability not only to determine the efficacy of stem cells, but to track the engraftment of stem cells based on the local environment using a single imaging modality.

**Gadolinium chelates**

As the first US FDA-approved MR contrast agents, gadolinium-chelated contrast agents have been widely used in off-label approaches to quantify myocardial perfusion and viability [33]. On T1-weighted MRI, cells labeled with paramagnetic gadolinium chelates appear hyperintense. Recently, a gadolinium-based contrast agent, Cy3-labeled gadofluorine M, has been used to label ESC-derived cardiac progenitor cells [34]. No effect on cell viability was observed in vitro and transplanted cells could be imaged in vivo 2 weeks post injection in both infarcted and normal mice [34]. Interestingly, this agent overcame the issue of intracellular compartmentalization of gadolinium in labeled cells, which results in smaller decreases in T1 relaxivity or decreased sensitivity to gadolinium-labeled cells [35]. Nonetheless, since unchelated gadolinium is highly toxic, concerns about clinical utilization of these agents for cell tracking remain.

**Superparamagnetic iron oxides**

Superparamagnetic iron oxide nanoparticles are the most widely used MR contrast agents for

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**Figure 2.** Registration of SPECT/CT with magnetic resonance images of the heart in a dog with a reperfused myocardial infarction receiving 111Indium oxine and superparamagnetic iron oxide-labeled mesenchymal stem cells. (A) Short-axis view of alignment of CT (gold) with MRI (grayscale) and SPECT (red) showing focal uptake in the septal region of the MI in a representative dog. (B) Focal uptake on SPECT (red) in another animal demonstrating localization of the mesenchymal stem cells (MSCs) to the MI in the (B) short-axis and (C) long-axis views. SPECT, due to the higher sensitivity, was able to detect the labeled MSCs whereas MRI failed to detect the superparamagnetic iron oxide particle-labeled MSCs. MI: Myocardial infarction. Reprinted with permission from [68].
cardiovascular applications, MR-based tracking of SPIO-labeled ESCs, mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs) have been performed in varied animal models [42–44]. In one study of SPIO-labeled mouse ESCs, the hypointensities in the ischemic myocardium were observed 4 weeks after implantation in mice, indicating the successful integration of labeled ESCs with infarcted myocardium [42]. In addition, intramyocardially injected SPIO-labeled MSCs could be detected by MRI up to 3 weeks after infarction in pigs (Figure 1) [45]. A similar study carried out by Amado et al. demonstrated substantial retention of SPIO-labeled bone marrow-derived stromal cells in infarcted myocardium at 8 weeks [45].

In an effort to take additional advantage of the lack of ionizing radiation with MRI and the ability to see the success of injections immediately, several groups have developed MR-compatible delivery devices often in combination with graphical interfaces for real-time MRI to perform MR-based stem cell delivery interventions [46–48]. At present, the regulatory hurdles for labeling stem cells are sufficiently large such that the addition of an investigational new device for delivery on an MRI platform that is not familiar to interventional cardiologists will probably limit the adoption of these techniques clinically in the near future.

Furthermore, beyond the normal limitations of direct cell labeling, such as possibility of signal dilution with cell replication and detachment of the label from the cell [49,50], the signal void generated by SPIOs may be problematic to distinguish from native tissue hypointensities, such as areas of ischemia, calcification and hemorrhage, motion artifacts and the presence of metallic objects (e.g., stents). To tackle this problem, a variety of positive-contrast MRI techniques or post-imaging processing methods (e.g., IRON, SWIFT and PARTS) [44,51–53] have been developed. However, the biggest hurdle to clinical adoption of these techniques is the removal of commercially available SPIO formulations. Nevertheless, preclinical studies of cardiac SPIO stem cell tracking will continue to be an active field that can be used to help guide clinical trials with respect to dosing, timing and cell choices with the caveat that any direct labeling scheme, such as SPIOs, may become detached from the cell of interest.

### Other MR contrast agents

In addition to 1H-based contrast labeling agents, other nonproton-based compounds containing 19F, 23Na or 13C have also been explored for MR
Detection. In particular, 19F-based agents have been used by several investigators for stem cell tracking [54–57]. Because there is essentially no native fluorine in the body, 19F ‘hot spot’ imaging [58] can be achieved with high sensitivity. However, specialized hardware and MRI sequences are often required to perform such studies.

■ MR reporter genes

MR reporter gene labeling may address the problems associated with direct MR contrast labeling. Several MR reporters have been developed, including creatine kinase [59], iron storage proteins (e.g., ferritin, transferrin and transferrin receptor) [23,32,60–63] and artificial proteins (e.g., lysine-rich protein) [64]. Overexpression of the transgenic human ferritin receptor and ferritin heavy chain subunit has been induced in tumor cells [32], neural stem cells [62] and ESCs [60]. Cardiac applications, however, have not yet been explored. Recently, preclinical studies have demonstrated the feasibility of labeling mouse skeletal myoblasts with the MR reporter ferritin. These transgenic cells were successfully detected by MRI in vitro and in vivo after transplantation into the infarcted mouse heart [23]. Besides safety concerns due to genetic alteration, the primary inherent problem with imaging of MR reporters is whether small numbers of cells can generate sufficient reporter gene products to enable visualization.

■ Direct radiolabeling

Direct cell labeling with 111In oxine ($t_{1/2} \approx 2.8$ days) developed for lymphocyte labeling has been adapted for cardiac stem cell imaging. For example, the trafficking of 111In oxine...
and SPIO-labeled MSCs could be monitored by clinical SPECT/CT up to 7 days in the infarcted canine myocardium, while MRI failed to detect the cells (Figure 2) [68]. Several other studies have demonstrated the varied retention of radiolabeled stem cells in the heart depending on the route of delivery, such as intravenous, intramyocardial, intracoronary and interstitial retrograde coronary venous delivery [69–76]. ¹¹¹In has also been used in patient studies to better understand the trafficking of peripheral blood progenitor cells after intracoronary and intravenous delivery in patients with heart disease [77,78]. ¹⁸F-FDG (t₁/₂ ~110 min) is another attractive radiotracer that is more readily available for stem cell labeling. The first human study demonstrated higher retention of ¹⁸F-FDG-labeled CD34-positive enriched bone marrow mononuclear cells in the infarcted myocardium than nonselected bone marrow cells 70 min after intracoronary delivery [79]. In a similar study, PET imaging revealed less than 3.3% of ¹⁸F-FDG-labeled HSCs accumulated within the infarcted myocardium at 2 h post-delivery [80]. Similar to MRI, which can provide viability and anatomical location information as well as cell tracking, dual isotope imaging, such as ¹⁸F-FDG or ⁹⁹mTc with ¹¹¹In, may be used to monitor cell migration relative to local tissue perfusion or metabolism [70,81].

Depending on the radiotracer used and cell type, minimum detection limits of direct radiotracer labeling vary from 2900 to 25,000 cells [82]. Major concerns of direct radiotracer labeling include the potential radiation damage to the cells [82–84], leakage of radiotracers over the time course [85], short imaging window due to radioactivity decay and radiotracer detachment from the cells such as direct MRI contrast labeling.

**PET/SPECT reporter gene labeling**

To date, three major PET/SPECT reporter genes, namely enzyme based, receptor based and transporter based, have been developed and applied to cardiac imaging in large animals or human studies. Examples include transporter-based sodium-iodide symporter (NIS) [86–88] for SPECT imaging, receptor-based dopamine type 2 receptor (D2R) [89–90] and the most commonly used enzyme-based herpes simplex virus type 1 thymidine kinase (HSV1-tk) or its mutant form HSV1-sr39tk [22] for SPECT/PET imaging.

The reporter probes for imaging thymidine kinase reporter genes are radiolabeled pyrimidine nucleoside analogs (such as ¹⁸F-FHBG and ¹²³I-FIAU/¹²⁴I-FIAU) and acycloguanosine. In a large animal model of myocardial infarction, Gyöngyösi et al. demonstrated the first successful translation of PET imaging of the HSV1-tk reporter gene to track cardiac stem cell biodistribution after intramyocardial injection using electromechanical mapping guidance (Figure 3) [91]. Enzyme-based PET reporter gene labeling has the advantage of signal amplification. Thus, a very low level of reporter gene expression or small number of transplanted cells can often be detected using radionuclide imaging. The major limitations include potential immune response elicitation to the foreign reporter gene product, limited reporter probe trapping due to rate limited probe transport into the cells and silencing of the reporter gene leading to inability to detect the transplanted cells [92]. In addition, leakage of the reporter probe from cells transfected with the reporter gene has also been reported with the NIS reporter gene [88]. Although radionuclide imaging shows a high sensitivity to a small number of cells, anatomical information is lacking. Thus, CT or MRI is needed to provide localization of cell distribution.

**Optical imaging**

Optical imaging techniques, including fluorescence imaging and bioluminescence imaging, can provide high sensitivity for cell tracking with detectability of 10⁻⁹ to 10⁻¹² mol/l and 10⁻¹⁰ to 10⁻¹⁷ mol/l, respectively [93]. In particular, optical imaging of reporter genes (e.g., green fluorescence protein or luciferase) can be used to monitor stem cell survival, proliferation and cardiac-specific differentiation in small animals [49,94]. However, technical challenges, such as the limited tissue penetration and low energy photon attenuation that restricts visualization of deep structures, such as blood vessels and the heart, limit development of clinical imaging systems [95,96].
Multimodality imaging

Multimodality imaging, such as the combination of CT with SPECT or PET, to obtain high sensitivity and anatomical detail can be expanded to other technologies to enhance stem cell tracking and measurement of cardiovascular function. A solution to some of the disadvantages of MRI, such as lack of MR compatible devices, poor physiological monitoring and limited temporal resolution for real-time interventions, would be to combine MRI with x-ray interventional techniques for stem cell delivery (Figure 4). Fusion of myocardial anatomy and viability maps from MRI in a swine infarction model have been used to target injections to the infarct borders using an x-ray fused with a MR registration platform [97]. Although stem cell labeling enables noninvasive visualization of cells in infarcted or normal subjects, a big concern for cardiac stem cell therapy is the significant cell death, which may be attributed, in part, to the ischemic environment and immunodestruction. To overcome early cell death, a hybrid technique whereby cells are encapsulated in a protective barrier (which blocks cell destruction by immunoglobulins and immune-mediated cells) and impregnated with imaging contrast agents is currently being explored [55,98,99]. By moving the labeling agents to the protective capsule rather than within cells, high contrast payloads for enhanced sensitivity can be used, which would often be cytotoxic. Recently, these imaging-visible microcapsules have been demonstrated in a swine heart (Figure 5) [100] and also used to track stem cells in a rabbit model of peripheral arterial disease (Figure 6) [101].

While these microencapsulation techniques, like direct labeling schemes, fail to measure cell viability, reporter gene labeling of the cells could be used to overcome this obstacle. At present, these microcapsules remain relatively large (~300–500 µm), therefore eliminating the possibility of direct intramyocardial or intracoronary injection. Furthermore, since the stem cells are trapped within the microcapsules, direct integration of the stem cells is prevented. Therefore, this technique will be most useful if stem cells are used to release cytokines to enhance angiogenesis and recruit native stem cells to differentiate into myocytes.

Conclusion

Stem cell labeling in conjunction with noninvasive imaging provides a powerful tool to aid in the optimization of stem cell type, selection dosing, delivery route and timing of transplantation to guide clinical cardiovascular stem cell trials. Despite significant progress in imaging techniques and label developments, no single labeling technique meets all the cardiac stem cell tracking criteria. A multimodality imaging
approach is likely to play an important role in illuminating different aspects of stem cell biology in vivo and elucidating the mechanisms of cardiac repair and regeneration.

Future perspective

For now, stem cell labeling for noninvasive tracking will remain mostly a preclinical tool to obtain FDA approval for new stem cell biologies and to guide the design of clinical trials. Since most interventional procedures are performed with x-ray angiographic systems, fusion of x-ray imaging with CT, MRI, PET or echocardiography appears the mostly likely imaging platform for cardiac stem cell tracking in clinical settings in the next 3–5 years. Ultimately, ultrasound, optical or MRI tracking of stem cells will be adopted for serial tracking of stem cells owing to the lack of ionizing radiation. Thus, long-term, future efforts will focus on delivery using existing technologies with the development of multimodality imaging approaches to interpret the results from cardiac stem cell trials and assess the long-term effects of stem cell labeling.

Financial & competing interests disclosure

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Tracking stem cells for cardiovascular applications in vivo

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SPECIAL REPORT


