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iREVIEW

STATE-OF-THE-ART REVIEW

Radionuclide Image-Guided Repair of the Heart

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ABSTRACT

As therapeutic approaches have evolved from exogenous bone marrow cell delivery to pharmacological stimulation of endogenous repair, so too has imaging of cardiac repair made significant strides forward. Evaluation of functional outcome remains a staple of noninvasive clinical imaging, which can robustly quantify contractile function, perfusion, and tissue viability. Direct labeling of cells or other novel therapeutics visualizes the whole-body distribution and pharmacokinetics of the therapeutic agent, providing insights into retention, targeting, and drug-tissue interactions. And finally, targeted molecular imaging agents are emerging that may be specifically coupled to drugs targeting the same pathway. This approach enables interrogation of temporal and spatial changes at the molecular level underlying tissue degeneration and regeneration, which facilitates accurate patient selection and timing for therapeutic intervention, as exemplified by recent efforts focusing on the role of inflammation in cardiac repair. The concept of image-guided repair carves out an important and evolving niche for molecular imaging in cardiovascular medicine, with the potential not only to predict outcomes but also to improve patient stratification and progress toward personalized reparative therapy. (J Am Coll Cardiol Img 2020;13:2415–29) © 2019 by the American College of Cardiology Foundation.

Short-term mortality after myocardial infarction (MI) has decreased because of advanced reperfusion therapy, but surviving patients are at increased risk for developing heart failure. Current therapies aim to modify the local tissue environment to support intrinsic repair (1). Novel therapies against diverse targets including inflammation have been successful in animal models but have yielded mixed results in clinical trials (2–5), raising questions about patient heterogeneity. Although imaging has typically assessed the functional outcomes of drug therapy, personalized precision therapy will require more sophisticated imaging indicators to distinguish molecular signatures of patients who may benefit from specific interventions. The evolution of reparative therapy presents an opportunity for noninvasive molecular imaging to provide critical insights into biologic mechanisms of disease and individual potential for repair, prior to the initiation of therapy. Image-based guidance of target and timing of novel reparative interventions, particularly by highly sensitive radionuclide imaging, may predict future clinical success. In this review we summarize the key concepts, practical needs, and future potential of radionuclide image-guided repair of the damaged heart.

EVOLUTION OF REPARATIVE THERAPY

Clinical implementation of evidence-based treatments during the past 20 years has resulted in prolonged patient survival after MI (6). Despite this success, patients with extensive myocardial damage

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ABBREVIATIONS AND ACRONYMS

BMC = bone marrow cell

CXCR4 = C-X-C chemokine receptor type 4

FDG = fluorodeoxyglucose

LV = left ventricular

LVEF = left ventricular ejection fraction

MI = myocardial infarction

MR = magnetic resonance

PET = Positron emission tomographic

RGD = arginine-glycine-aspartatic acid

RNA = ribonucleic acid

or severely reduced left ventricular (LV) ejection fraction remain at risk for developing progressive LV remodeling and chronic heart failure (7). However, a large MI and reduced LV ejection fraction (LVEF) are neither necessary nor sufficient for adverse remodeling to occur. Indeed, some patients with small MIs and nearly normal LVEFs have adverse remodeling, whereas other patients with larger MIs and reduced LVEFs do not. Routine cardiac imaging using echocardiography or contrast-enhanced cardiac magnetic resonance (MR) imaging therefore has limited value in discriminating patients with MI with favorable or unfavorable outcomes (8).

Acute MI triggers an intense inflammatory response in which divergent leukocyte populations coordinate tissue repair. Initially, neutrophils and inflammatory monocytes are recruited to the infarcted area to remove dead cells and matrix debris. Excess early inflammation and proteolytic digestion, however, may injure surviving cardiomyocytes in the border zone and promote infarct expansion by reducing the tensile strength of the necrotic area. Later, accumulated monocytes give rise to reparative macrophages that proliferate locally and promote neovascularization and scar formation (9). Macrophages also accumulate in the noninfarcted myocardium after MI, either by resident macrophage proliferation or differentiation from recruited monocytes (10). Interventions that limit cardiac recruitment of monocytes late after MI attenuate LV remodeling and chronic heart failure, indicating that the net effect of recruited monocytes in the remote myocardium may be detrimental (10).

Identification of inflammatory and reparative myeloid cell subsets currently relies on flow cytometric analysis of cell surface markers; however, this nomenclature is in flux (11). Indeed, up to 7 macrophage subsets can be identified by single-cell ribonucleic acid (RNA) sequencing in infarcted mouse hearts, although it remains unknown whether all these subsets diverge functionally (12). Adding further complexity, monocyte mobilization and recruitment and macrophage differentiation and function after MI are controlled by dendritic cells, regulatory T cells, and B cells (13–15).

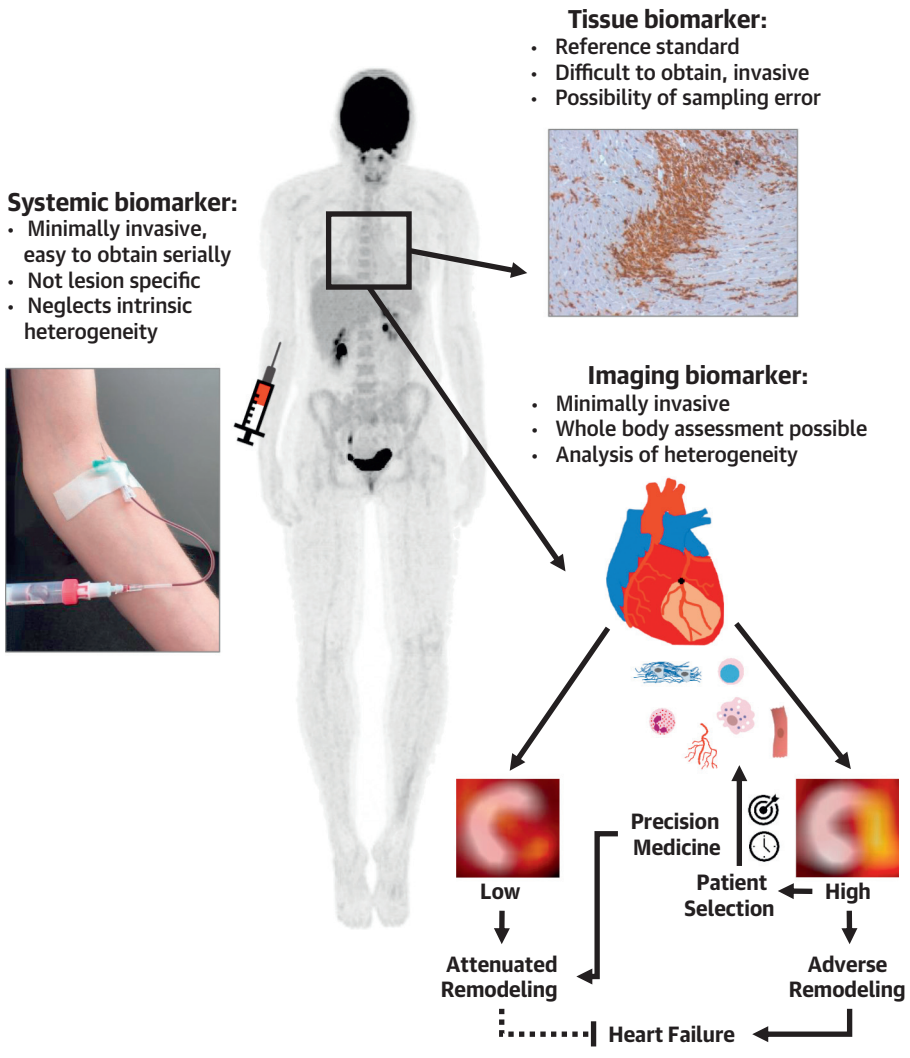
Although the biphasic monocyte/macrophage response was first observed in mice, similar inflammatory and reparative myeloid cell subsets have been described in patients with acute MI or chronic heart failure (16–18). Individual differences in the intensity or quality of the inflammatory response are thought to predispose or protect patients from adverse remodeling (8). As discussed later, new imaging biomarkers of the complex cellular choreography of infarct repair may help define heterogeneities in patient inflammatory responses.

Animal studies indicate that the inflammatory and reparative cascades after MI must be tightly regulated to achieve optimal outcome, defined by a small and durable scar, preserved LV geometry and function, and long-term survival. Broad anti-inflammatory strategies (e.g., using glucocorticoids, nonsteroidal anti-inflammatory drugs, or methotrexate) did not promote beneficial effects or even were associated with adverse outcomes in early clinical trials (19). These failures stimulated the development of more specific therapies aimed at identifying and curbing excess inflammation or enhancing tissue repair. In CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study), treatment with an interleukin-1β-neutralizing antibody reduced the risk for recurrent vascular events and heart failure hospitalizations in patients with previous MI and persistent inflammation, as indicated by elevated high-sensitivity C-reactive protein levels (2). CANTOS provides a proof of concept for targeted anti-inflammatory strategies in patients with cardiovascular disease.

Although CANTOS did not study patients with acute MI, neutralizing interleukin-1β attenuates inflammatory monocyte recruitment and adverse LV remodeling in apolipoprotein E-deficient mice with acute MI (20). Likewise, nanoparticle-facilitated silencing of C-C chemokine receptor type 2 in monocytes or silencing adhesion molecules in endothelial cells attenuates adverse remodeling in these mice, which are known to have exaggerated inflammation after MI (21). Pharmacological C-X-C chemokine receptor type 4 (CXCR4) blockade provides another promising strategy to curb excess inflammation after MI (22). This treatment attenuates inflammatory gene expression in monocytes and macrophages via enhanced regulatory T cell mobilization and recruitment (22).

Injection of autologous bone marrow cells (BMCs) into the infarct border zone is associated with modest but reproducible improvements in cardiac function in animal models of acute MI (23). The initial premise of heart muscle regeneration by the transdifferentiation of bone marrow (stem) cells has been disproved (24). Instead, paracrine or immune-modulatory effects on tissue repair have been proposed as a conceptual mechanism of this benefit. Clinical trials investigating

FIGURE 1 **Biomarkers to Guide Targeted Therapy**

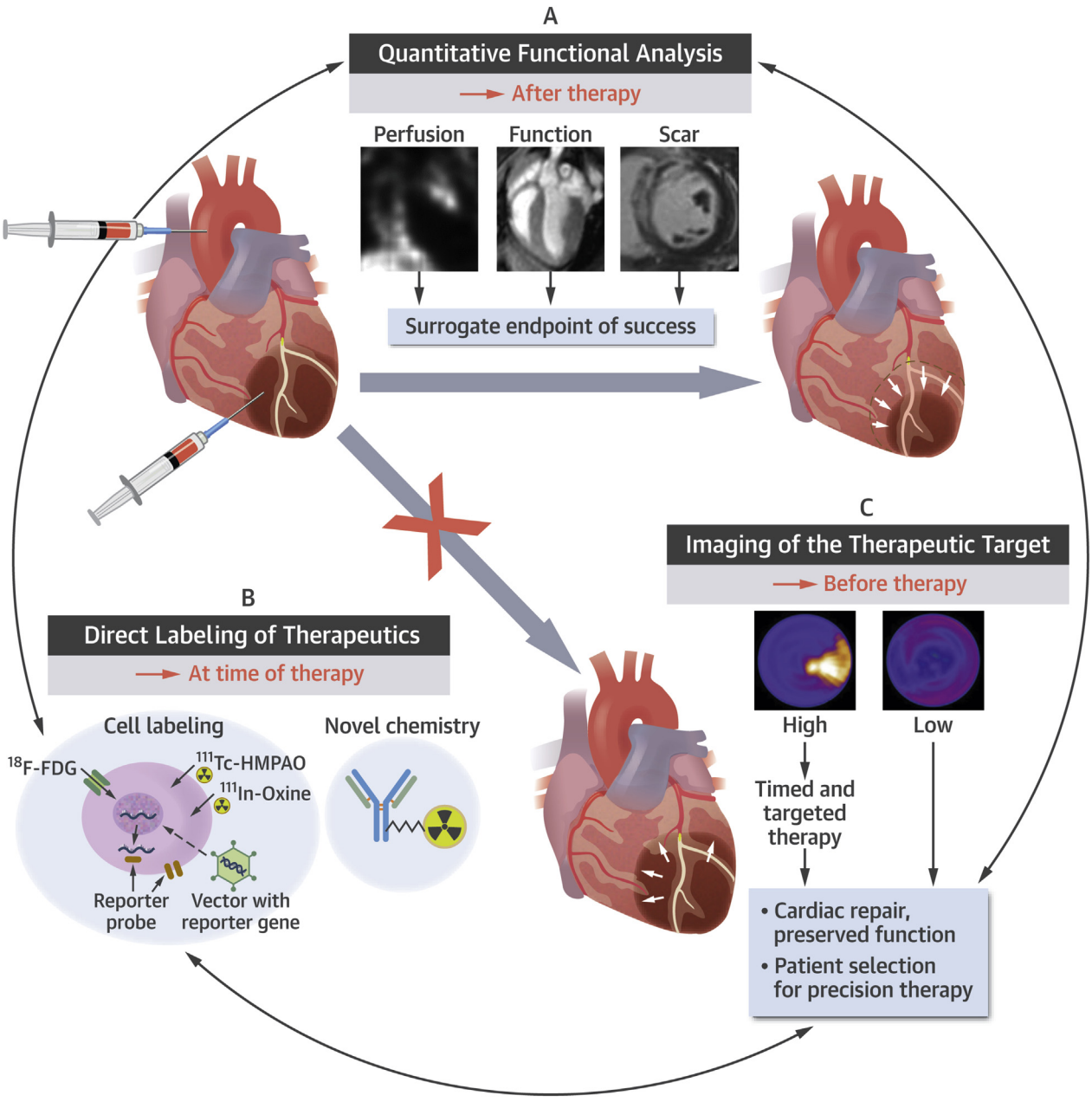


The reference standard for the assessment of cardiac disease biomarkers is a tissue biopsy, which is invasive, difficult to obtain, and may not be representative for the whole myocardium. One alternative is assessment of blood biomarkers (liquid biopsy), which is minimally invasive and can be obtained serially but is not lesion specific and neglects intrinsic heterogeneity. Accordingly, imaging biomarkers are emerging (virtual biopsy), which are minimally invasive and allow interrogation of the whole body and tissue regional heterogeneity. Imaging biomarkers may precisely select patients for new, targeted molecular therapies for precision medicine.

the efficacy of BMC therapy after MI have produced mostly neutral results, however (25). Systemic application of BMC-derived secreted proteins, such as myeloid-derived growth factor, or therapeutic inhibition or application of noncoding RNAs and exosomes may enable more specific biologic approaches to improving tissue repair and heart function after MI (26–28). Inclusion of patients into clinical BMC trials was based solely on low LVEF, and with current treatment strategies, many such patients do well after MI. Clinical translation of new anti-inflammatory or reparative strategies will therefore require better identification of patients in need of such additional therapies.

Additional pathophysiologic processes influence the progression of heart failure and repair after initial ischemic insult, including neurohormonal activation, vascular remodeling, angiogenesis, fibrosis, and ventricular remodeling (29). Although current and emerging therapies target these mechanisms, the

CENTRAL ILLUSTRATION **Image Guidance of Cardiac Repair**



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Conventional cardiac imaging measures parameters such as myocardial perfusion (single-photon emission computed tomography or positron emission tomography), scar composition (magnetic resonance [MR]), or left ventricular function (e.g., MR) as surrogate endpoints of therapeutic success (imaging after therapy). Nuclear imaging methods may also directly label therapeutic agents such as cells or antibodies (imaging at the time of therapy) to track distribution. More recently, initial studies have explored cardiac molecular imaging to directly guide new molecular targeted agents to treat the right patient with the right drug at the right time (imaging before therapy).

TABLE 1 Clinical Imaging Tests Predictive of Adverse Outcome and Potentially Useful as Surrogate Endpoints for Determining the Success of Cardiac Repair

Physiological Parameter	Modality	Tracer/Technique
Ventricular function / geometry	Echocardiography, CMR (PET, SPECT, CT)	Cine, ECG gating
Ischemia	SPECT, PET, CMR (CT, echocardiography)	Perfusion tracers, contrast agents
Myocardial blood flow / flow reserve	PET (CMR, SPECT)	Modeling of perfusion marker kinetics
Infarct size, scar	CMR (PET, SPECT)	Delayed enhancement, perfusion defect
Edema	CMR	T2 mapping
Hibernation	PET	FDG (glucose use)
Cardiac efficiency	PET	Acetate (oxidative metabolism)
Sympathetic innervation	SPECT, PET	Catecholamine analogues

CMR = cardiac magnetic resonance; CT = computed tomography; ECG = electrocardiographic; FDG = fluorodeoxyglucose; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

timing of post-infarct inflammation (i.e., within the first week after damage) is particularly suited to image-guided repair of the heart.

ENVISIONED ROLE OF TARGETED IMAGING BIOMARKERS FOR THERAPY GUIDANCE

As exemplified by BMC trials and CANTOS, current patient selection for novel therapies to support myocardial repair relies on imaging parameters of LV function and on blood-derived biomarkers. Because impaired global LV function is a nonspecific cardiac endpoint, it does not match the specificity of most novel molecular-targeted drugs and may therefore be of limited value for precise patient selection. Blood-derived biomarkers provide more specificity for the systemic activation of certain targetable biomechanisms. For example, inflammation severity may be gauged from leukocyte count and C-reactive protein, which have established value for predicting cardiac functional outcomes (30,31). Yet blood-derived biomarkers reflect systemic activation and do not provide direct information on intensity, localization, and heterogeneity in the target organ and interconnected regions. Biopsy and histological analysis could provide localized information, but this approach is invasive, difficult to apply serially, and compromised by potential regional sampling errors. Here, molecular imaging using radiotracers targeted to specific biomechanisms has several unique features and advantages, including its noninvasive nature, serial imaging feasibility, and provision of regional information for the heart as the target organ and other regions of the whole body, providing in essence a "virtual biopsy" (**Figure 1**). This delivers a spectrum of options for image-guided cardiac repair. First, imaging may stratify patients by therapeutic target expression, effectively identifying optimal patient populations for therapy. Second, molecular imaging may identify the appropriate timing for intervention (e.g., when expression of the drug target is maximal in the damaged tissue). Third, the therapeutic agent may be radiolabeled and followed directly, to determine its in vivo fate and its interaction with the target tissue. And last, serial imaging can monitor the physiological and biologic changes in response to therapy, providing exquisite and early identification of therapeutic efficacy.

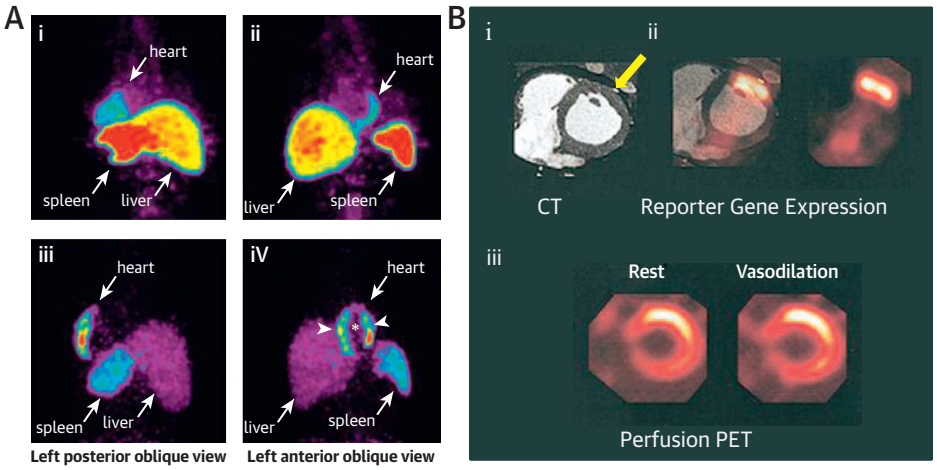
The common goal and vision of using molecular imaging for guidance of myocardial repair are to promote personalized therapy. By better identifying suitable patient populations and directly monitoring therapy success, drug development and clinical translation may be accelerated using image-based endpoints in experimental and clinical research (32). This will include a toolbox of established conventional imaging parameters along with directly labeled therapeutic agents and novel molecular tracers characterizing the biologic target of novel drug interventions (**Central Illustration**).

QUANTIFYING FUNCTIONAL DISEASE STATE AND OUTCOME OF REPARATIVE THERAPY

Routine clinical imaging assays may be used to define the degree of cardiac compromise and the likelihood of disease progression. They may also be applied serially to measure the response to reparative therapy.

Commonly, assessment of LV function and geometry using echocardiography, MR, electrocardiographically gated computed tomography, or nuclear imaging studies (33–35) is a frequent endpoint in clinical trials of myocardial repair (36–39) and a powerful predictor of mortality. Cardiac MR can also assess infarct composition by late gadolinium enhancement (40) or T2-weighted edema imaging (41) to predict late cardiac functional recovery (42).

FIGURE 2 Labeling of Therapeutics to Investigate Their Biodistribution



(A) Positron emission tomographic (PET) imaging 65 to 70 min after coronary infusion of ^{18}F-fluorodeoxyglucose (FDG)–labeled cells in patients demonstrated significantly lower myocardial homing of unselected bone marrow cells **(i, ii)** compared with CD34-enriched bone marrow cells **(iii, iv)**. Cell accumulation was highest within the infarct border zone **(arrowheads)** but not within the infarct center **(asterisk)**. Modified with permission from Hofmann et al. (47). **(B)** PET/computed tomographic (CT) short-axis images after myocardial injection of a vascular endothelial growth factor (VEGF) gene therapy. **(i)** CT imaging–visualized titanium clip at injection site of adenoviral vector encoding herpes simplex virus thymidine kinase (HSV-tk) PET reporter gene and VEGF proangiogenetic gene. **(ii)** PET imaging with ^{18}F-fluoro-hydroxymethylbutyl-guanine (FHBG) demonstrated myocardial HSV-tk expression, and **(iii)** ^{13}N-ammonia PET imaging showed higher perfusion around the injection site responding to VEGF expression. Modified with permission from Wagner et al. (51).

Rest-stress myocardial perfusion imaging provides scar size, function, and microvascular information via flow reserve, as evidenced in a recent gene therapy study after MI (43).

Table 1 summarizes established noninvasive translational and clinical imaging tests that are predictive of long-term outcomes and accordingly may be used for the assessment of baseline status and therapeutic response in studies of cardiac repair. Importantly, these routine clinical tests do not provide direct insight into the individual biology related to cardiac repair. Directly labeling therapeutic agents or visualizing the specific target of reparative intervention may overcome these limitations.

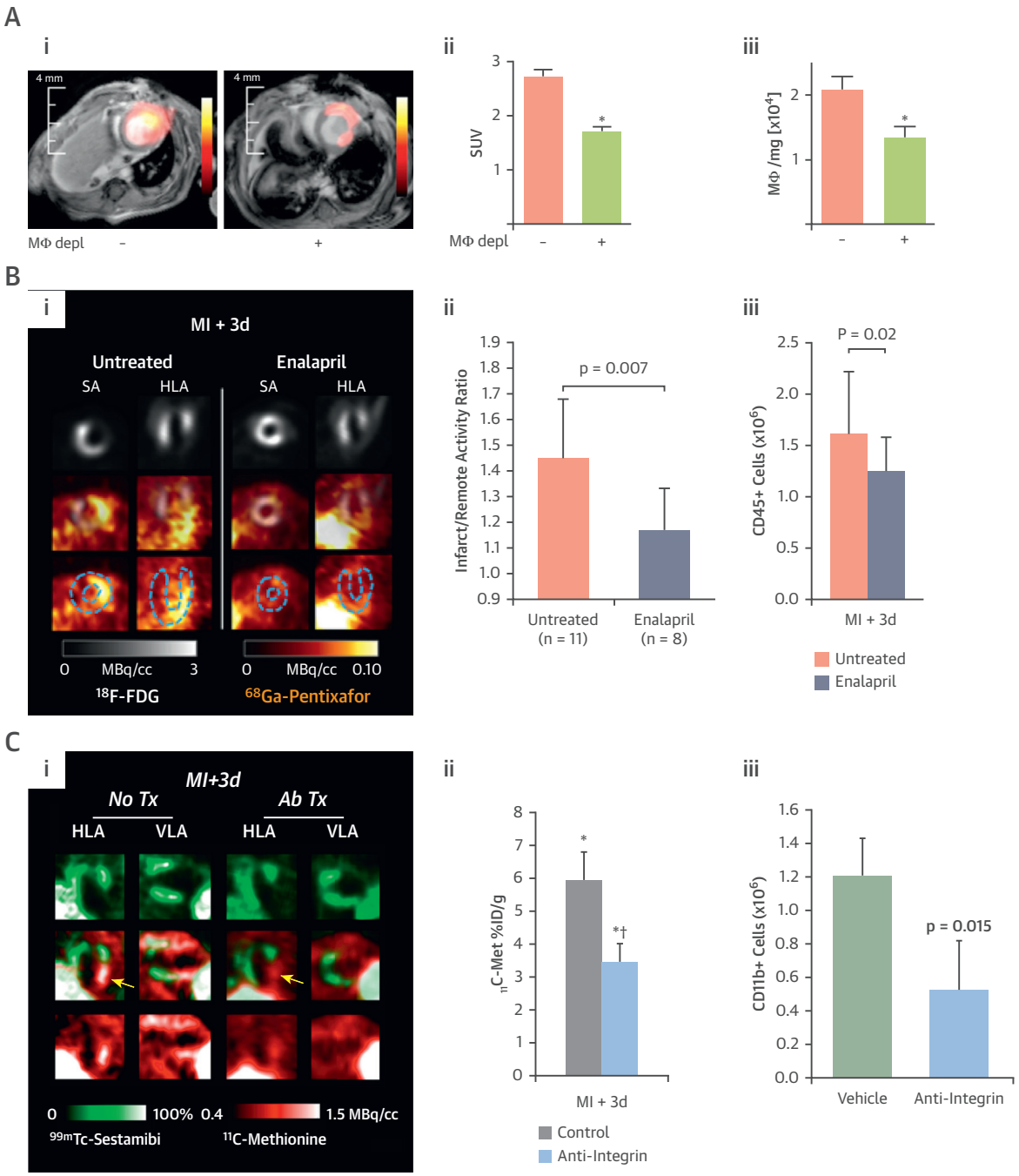
DIRECT LABELING OF THERAPEUTICS FOR IN VIVO PHARMACOKINETICS

A second application of imaging in cardiac repair is to directly track the distribution and retention of the therapeutic agent (Figure 2). Labeling of exogenously delivered cells before their application allows tracking of cell distribution and retention. Analogously, simplified chemistry methods for labeling novel therapeutic antibodies and peptides allow investigation of pharmacokinetics in vivo. Nanoparticle or microbubble constructs may facilitate targeted delivery of therapeutic payloads and simultaneous detection by computed tomography, MR, or ultrasound (44,45). Incorporation of targeting moieties into the inert nanoparticle surface enhances the drug efficacy at the target site (45).

DIRECT CELL LABELING AND TRACKING. Transplanted cells may be directly radiolabeled for tracking by positron emission tomographic (PET) or single-photon emission computed tomographic imaging to assess homing, retention, engraftment, and efficacy for repair (46-48). Such studies demonstrated low retention of therapeutic cells in clinical settings, with maximum <10% retention (49). Although confounding factors such as label efflux, induction of cell death, and functional impairment should be considered, direct cell labeling can optimize cell delivery, though the time window for analysis is limited (50).

REPORTER GENE IMAGING. To extend this time frame, genetic modification of therapeutic cells to express a reporter gene facilitates specific accumulation of an injectable radiolabeled reporter probe. The advantages of this approach are the feasibility of repeated imaging over a longer time period, the direct link between signal and cell viability (reporter gene

FIGURE 3 **Imaging of the Therapeutic Target**



(A) Cardiac positron emission tomography/magnetic resonance with ^{18}F-fluorodeoxyglucose (FDG) 5 days post-myocardial infarction (MI) under ketamine/xylazine anesthesia to suppress cardiomyocyte uptake. **(i)** ^{18}F-FDG accumulated in the infarct territory, and macrophage depletion (MΦ depl) significantly lowered the uptake **(ii)** proportional to fluorescence-activated cell sorting-derived macrophage (MΦ) numbers in the infarct **(iii)**, supporting macrophages as the main cellular basis of ^{18}F-FDG signal. Modified with permission from Lee et al. (62). **(B)** $_{68}$Ga-Pentixafor (color scale) identified inflammation 3 days post-MI in the ^{18}F-FDG-defined infarct (grayscale) in mice **(i)** and monitored anti-inflammatory treatment. Enalapril led to significantly lower pentixafor uptake at 3 days **(ii)**, in parallel with significantly lower CD45-positive leukocytes in the left ventricle **(iii)**. Modified with permission from Thackeray et al. (70). **(C)** $_{11}$C-Methionine **(red)** identified inflammation in the ^{99m}Tc-sestamibi **(green)** defined infarct **(arrow)** at 3 days post-MI in mice **(i)** and effectively monitored blockade of inflammatory cell extravasation by therapeutic antibodies against integrins. Anti-integrin blockade significantly lowered methionine uptake **(ii)** and CD11b$^+$ cell accumulation **(iii)** in the infarct territory. Modified with permission from Thackeray et al. (67). Ab = antibody; CCR2 = C-C chemokine receptor type 2; HLA = horizontal long axis; ID = injected dose; KO = knockout; SA = short axis; SUV = standardized uptake value; Tx = therapy; VLA = vertical long axis.

expression is restricted to viable cells), and the potential to monitor cell engraftment and potentially its progeny. Several reporter genes have been investigated in cardiology, including herpes simplex virus thymidine kinase, sodium-iodide symporter, and dopamine D2 receptor (50). Notably, reporter gene transfer may be coupled to a therapeutic gene (51), such that the reporter construct provides a surrogate indication of gene therapy. Issues related to safety and potential adverse long-term effects on cell integrity need to be considered, and the target-to-background ratio is lower than for directly labeled cells, because of systemic administration of the reporter probe (50). Still, given recent advances in gene transfer methodology (52), reporter-gene imaging is expected to grow for cell tracking and as a readout of gene therapy.

LABELING OF ANTIBODIES, PROTEINS, PEPTIDES, AND RNAs. Building on advances in radiolabeling technology, direct labeling of the therapeutic agent may also be applied to novel drugs. The small peptide-based chemical structures of endogenous macromolecules and synthetic drugs are poorly conducive to conventional radiolabeling because of their sensitivity to typically harsh labeling conditions. Click chemistry (i.e., rapid and efficient reactions at ambient temperatures under mild conditions) is ideally suited to radiochemistry applications with short-lived isotopes (53). Specifically, click chemistry reactions allow site-specific bioconjugation, prosthetic group attachment, novel chelation architecture, and pre-targeting approaches, which now have established utility, primarily in oncology applications (54,55).

With the parallel growth of monoclonal antibody therapies in cardiovascular disease (56), direct labeling of antibodies may allow their tracking in cardiac repair. Truncation of antibody structure to microbodies or nanobodies significantly reduces blood circulation time in vivo, which may lower background and optimize image contrast (57). Labeling of camelid single-domain antibody fragments targeted to mannose receptor using ^{18}F demonstrated specific binding to macrophages in tumors, with favorable imaging kinetics (55). Potential utility for cardiovascular disease has not been established but is an opportunity given the role of mannose receptor in cardiovascular pathology (58).

More recently, molecules targeting micro-RNAs have been designed, incorporating oligonucleotide sequences targeted to specific micro-RNAs and conjugated to a radiometal chelator. Initial studies in healthy rats demonstrated extended retention in the epiphysis of long bones and bone marrow (59). Although this proof of concept demonstrates feasibility, additional studies are needed to determine the validity of such compounds in cardiovascular disease conditions. Nevertheless, interest in micro-RNA-based therapeutics provides an opportunity for molecular imaging in drug development (60).

Taken together, direct labeling of therapeutic agents can provide valuable insights on the distribution, efficacy, and elimination of the drug, which may help optimize dosing for individual patients. These approaches are therefore powerful yet underused tools for the development, translation, and clinical implementation of agents aiming at cardiac repair.

SPECIFIC MOLECULAR IMAGING OF THE THERAPEUTIC TARGET

The most recent and emerging imaging approach in reparative cardiovascular medicine is direct visualization of therapeutic molecular pathways. Direct radiolabeling of the therapeutic agent enables pharmacokinetic analysis of the drug but rarely yields diagnostic radiotracers with robust and quantitative features for imaging of a biologic target. This is due to different kinetic requirements of a diagnostic tracer versus a therapeutic drug (i.e., rapid, high-affinity, and high-contrast target accumulation at tracer doses vs. stable, longer acting binding at pharmacological doses). Accordingly, a spectrum of specific tracers targeting biomechanisms of repair has been introduced and is under development. Although image-guided targeted therapy is aggressively pursued in oncology for improved precision in individualized treatment with expensive agents, image-guided molecular therapy is just emerging in cardiology. The advent of novel specific therapeutic agents that require guidance to the right time and the right patient is a key stimulus for implementation of new imaging approaches to visualize mechanisms involved in tissue repair (**Figure 3**). **Table 2** summarizes specific imaging assays that characterize the myocardial substrate for tissue repair and hold potential for image guidance of cardiac reparative therapy. Inflammation after MI is an attractive imaging target, with numerous targeted radiotracers under investigation to noninvasively monitor leukocyte mobilization, as reviewed elsewhere (32,61). The ubiquity of inflammation in cardiovascular disease and its emergence as a prominent therapeutic and imaging target render it a functional test case for imaging cardiac repair. Moreover, the time course of post-infarct inflammation (i.e., over 7 days after MI)

TABLE 2 Examples of Specific PET Imaging Tests That Characterize the Myocardial Molecular Environment Susceptible to Cardiac Reparative Therapy Via the Same Pathway

Molecular Target	Diagnostic Tracer	Matched Therapy
CXCR4	^{68}Ga-pentixafor	AMD3100, POL5551
TSPO	^{18}F-GE180, ^{11}C-PK11195, ^{11}C-PBR28, ^{11}C-DPA-713	PK11195, lorazepam, 4′-chlorodiazepam
CCR2	^{68}Ga-DOTA-ECL1i	CCX872, Pf-04634817
SSTR2	^{68}Ga-DOTA-Tate	Octreotide, lanreotide
Phagocytosis	^{18}F-polyglucose nanoparticle	Therapeutic nanoparticles
MMP	^{18}F-IPFP (^{111}In-RP782)	TIMP analogues
Integrin $a_v\beta_3$	^{18}F-galacto-RGD, ^{18}F-fluciclatide, ^{18}F-RGD-K5, ^{18}F-alfatide, ^{68}Ga-NOTA-RGD	Vascular growth factors
Fibroblast activation protein	^{68}Ga-FAPI	RO6874281

CCR2 = C-C chemokine receptor type 2; CXCR4 = C-X-C chemokine receptor type 4; MMP = matrix metalloproteinase; PET = positron emission tomography; RGD = arginine-glycine-aspartatic acid; SSTR2 = somatostatin receptor 2; TIMP = tissue inhibitor of matrix metalloproteinase; TSPO = 18-kD translocator protein.

accommodates image-guided therapy. The development from basic tracer implementation toward guidance of specific targeted therapies is described later, with a specific focus on radionuclide-based inflammation imaging.

STEP 1: TRACERS FOR DETECTING INFLAMMATORY CELLS AND PATHWAYS. Inflammation is an early and complex response to any tissue injury, which sets the stage for subsequent repair and healing. The broad range of immune mediators and cells and temporal dynamics necessitate precise timing and patient selection for effective intervention.

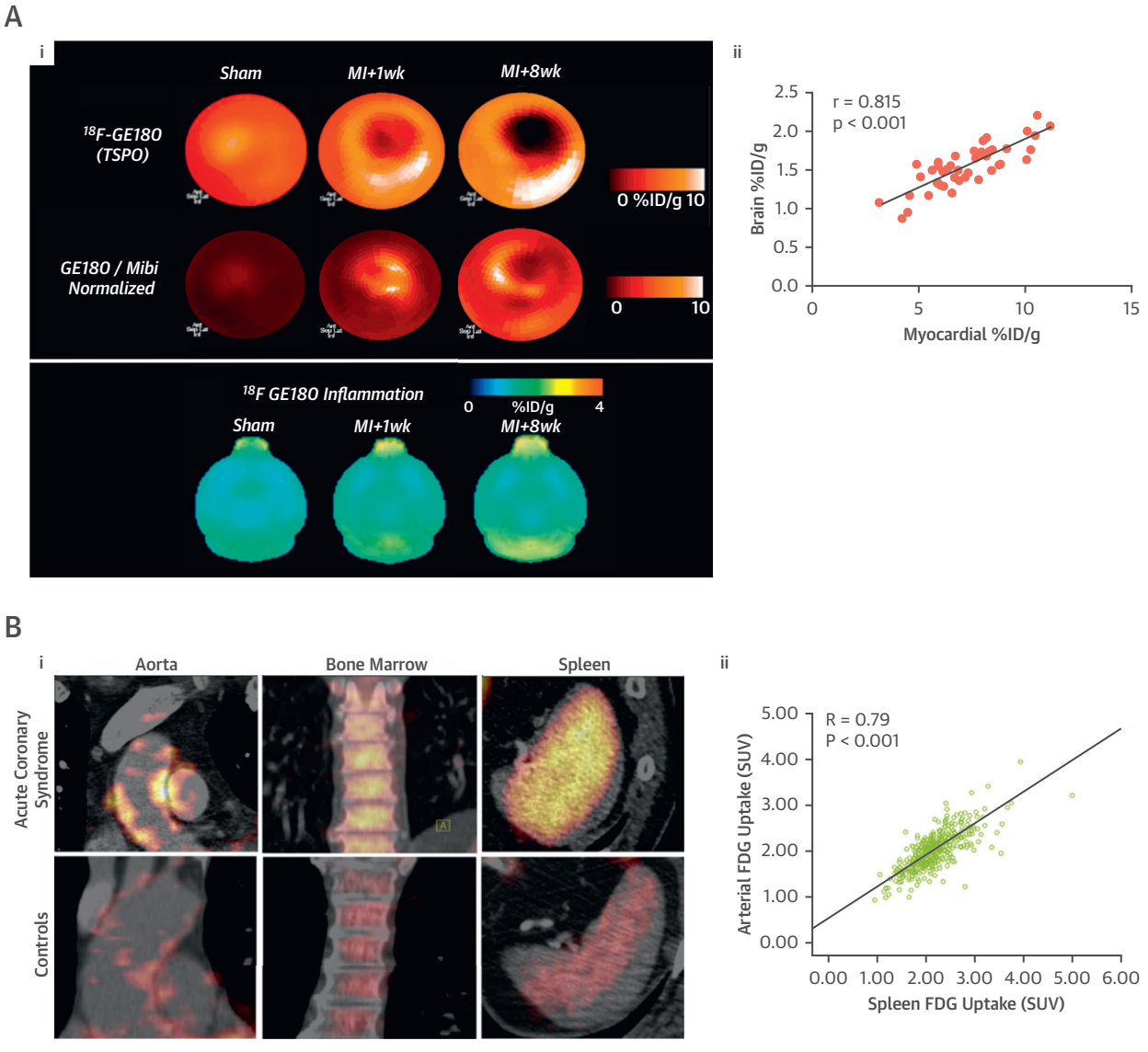
High metabolic rate of inflammatory leukocytes allows the use of ^{18}F-fluorodeoxyglucose (FDG) to delineate inflammation in the infarct territory. High infarct ^{18}F-FDG uptake by monocytes and macrophages was detected at 5 days post-MI (62). Robust cardiomyocyte ^{18}F-FDG signal necessitates nonphysiological suppression to isolate the inflammatory signal (63,64). Stressed or ischemic cardiomyocytes exhibit elevated glucose utilization, which may be more difficult or impossible to suppress (65), compromising the specificity of ^{18}F-FDG signal.

Amino acid metabolism and protein turnover represent such alternative targetable processes. Local ^{14}C-methionine accumulation was observed on multitracer autoradiography, colocalized to the ^{201}Tl-defined infarct and CD68$^+$ macrophage content early after reperfused MI in rats (66). Application in mice after permanent coronary occlusion demonstrated ^{11}C-methionine PET signal 3 days after MI that was significantly lowered by blocking leukocyte extravasation (67). However, the short-lived ^{11}C isotope has prevented more widespread use of ^{11}C-methionine for inflammation imaging, as tracers with longer lived PET isotopes such as ^{18}F or ^{68}Ga are preferable.

Early inflammatory cell mobilization and recruitment are orchestrated by cytokines and chemokines, potential therapeutic targets (56). Expressed by a variety of leukocytes and progenitor cells, CXCR4 can be imaged using the specific ligand ^{68}Ga-pentixafor (68,69). PET imaging in mice revealed specific binding of ^{68}Ga-pentixafor in the infarct territory 3 days after MI, declining by 7 days, proportional to total ventricular leukocytes assessed using flow cytometry (70). Comparable CXCR4 up-regulation has been reported in patients in the first week post-infarct (70), though the signal is variable, suggesting patient heterogeneity and supporting the notion that different subgroups may respond differently to inflammation-targeted interventions. Alternative chemokine receptors can provide broader perspective on inflammation. Specifically, C-C chemokine receptor type 2-targeted ^{68}Ga-DOTA-ECL1i demonstrated robust uptake in the infarct territory after MI in mice (71), providing insights into monocyte trafficking. Additionally, mitochondrial translocator protein, overexpressed by activated macrophages and activated microglia, has identified peripheral inflammation in atherosclerosis and acute MI (72,73). Further tracers of specific components of post-injury inflammation include the somatostatin receptor ligand ^{68}Ga-dotatate (74) or the macrophage-avid ^{18}F-polyglucose nanoparticle (75). A variety of promising tracers have been preclinically investigated for myocardial imaging, albeit with limited clinical characterization. Larger prospective clinical feasibility studies will help demonstrate benefit over ^{18}F-FDG and reliability for routine clinical application.

STEP 2: LINKING EARLY INFLAMMATION IMAGING BIOMARKERS WITH SUBSEQUENT ADVERSE FUNCTIONAL OUTCOMES. To justify the use of an image-based molecular biomarker, the imaging signal should predict adverse functional outcomes. Evidence of prognosis is beginning to emerge for various tracers. In a clinical study, ^{18}F-FDG PET/MR imaging at 5 days

FIGURE 4 Systems Biology



(A) Whole-body small-animal positron emission tomographic (PET) imaging with ^{18}F-GE180 identified post-infarct myocardial inflammation by targeting translocator protein (TSPO) and detected parallel neuroinflammation at 1 week after myocardial infarction (MI) **(i)**. At 8 weeks after MI, the remodeled remote myocardium displayed TSPO up-regulation with concurrent microglial activation. Normalization of PET scans to ^{99m}Tc-sestamibi perfusion demonstrated TSPO up-regulation in the infarct at 1 week and in remote myocardium at 8 weeks after MI. $_{18}$F-GE180 uptake in heart and brain exhibited a strong correlation **(ii)**. Modified with permission from Thackeray et al. (73). **(B)** Patients with acute coronary syndrome (ACS) exhibited systemic inflammatory activation as assessed using ^{18}F-FDG compared with control subjects **(i)**, with a strong relationship between arterial and splenic signal **(ii)**. Modified with permission from Emami et al. (92). ID = injected dose; SUV = standardized uptake value.

after reperfused acute MI identified variable inflammation in the myocardium, which was inversely proportional to cardiac functional outcome at 6 months, independent of infarct size (38). On regional analysis, the extent of the ^{18}F-FDG-positive area exceeded the scar defined by MR late gadolinium enhancement, with closer colocalization to the single-photon emission computed tomographic perfusion defect. The investigators concluded that the early ^{18}F-FDG signal more accurately reflected area at risk than scar, though the relative contribution of inflammatory cells and stressed border zone myocardium to

the signal remains unclear. Further work with more specific inflammation-targeted radiotracers may provide additional information. Indeed, myocardial ^{18}F-GE180 translocator protein PET signal early after MI in mice independently predicted subsequent cardiac remodeling and progressive heart failure (73). Although promising, these preclinical results require confirmation in patients as a next step toward clinical implementation of targeted inflammation imaging after infarction.

STEP 3: LINKING INFLAMMATION IMAGING BIOMARKERS TO THERAPEUTIC AGENTS. A last step toward image-guided cardiac repair is to apply prognostic molecular imaging to select patients at highest risk and modify this risk to improve outcome. This is perhaps one of the most powerful opportunities enabled by molecular imaging, based on the ability to quantitatively assess temporal presence and magnitude of therapeutic target expression. Ideally, the molecular target for imaging and the target (or even molecule) for therapy are identical for precise guidance. This concept is exemplified in oncology, in which identical chelator constructs may be used for imaging and delivery of radiotherapy using a theranostic approach (76), but it may also be applied for image-based guidance of nonradioactive therapeutics (22,70).

Image-based guidance may also help resolve the observation that new promising preclinical therapies sometimes exhibit minimal to no efficacy in first clinical studies (19), emphasizing the need for careful selection of a homogeneous, individually characterized study group. One example is concurrent imaging and treatment of the stromal cell-derived factor 1α-CXCR4 chemotactic signaling pathway involved in the recruitment of bone marrow–derived leukocytes to the site of injury (77). After MI, stromal cell-derived factor-1α is highly up-regulated within the hypoxic myocardium and together with its receptor CXCR4 is cardioprotective (78). A single dose of the CXCR4 blocker AMD3100 reduced infarct size, increased progenitor cell recruitment and angiogenesis, and decreased macrophage recruitment, leading to improved cardiac functional outcomes. In contrast, continuous blockade of CXCR4 did not improve long-term outcomes (79). More recently, splenic regulatory T cells have been identified as mediating the positive effects of CXCR4 blockade after ischemia/reperfusion in mice (22). Using CXCR4 PET imaging to identify the appropriate intervention timepoint by peak signal, on-peak blockade may optimally support infarct healing and prevent adverse remodeling. This concept requires preclinical and clinical validation, but oncology experience supports feasibility (76), and translational challenges for targeted molecular therapies highlight the need.

ALTERNATIVE IMAGING-THERAPY TARGETS FOR CARDIAC REPAIR

Although imaging and therapy for inflammation are perhaps most advanced, additional pathophysiologic and repair processes such as thrombosis, angiogenesis, and fibrosis contribute to ventricular remodeling. Novel radiotracers and therapies are emerging that may fit the same paradigm.

Imaging of thrombosis using targeted ligands of glycoprotein (GP)-1 IIb/IIIa to denote platelet aggregation has demonstrated increased signal in large animal models of vascular disease and thromboembolism in humans (80,81). The growing use of GP-1 IIb/IIIa inhibitors for acute coronary syndrome may provide an avenue for repair, but the requirement for urgent application may be suboptimal for image-based guidance.

Enhanced angiogenesis is characteristic of cardiac repair following injury. Cell therapy studies have demonstrated elevated binding of radiolabeled arginine-glycine-aspartatic acid (RGD) peptides indicative of higher $\alpha_v\beta_3$ integrin expression and neovascularization of the infarct territory over 2 weeks after MI (82). Heterogeneity in cell therapy studies is likewise reflected in the RGD signal response (83). Indeed, the RGD signal may also reflect active inflammation (84,85). Despite extensive preclinical evidence, clinical RGD imaging experience remains limited.

Extracellular matrix reorganization, especially via matrix metalloproteinases, can indicate remodeling and repair. Preclinical imaging of matrix metalloproteinases has demonstrated potential for monitoring myocardial health (86), but wider applications remain elusive.

New techniques to image activated myofibroblasts offer the opportunity to precisely monitor fibrosis. CMR with late gadolinium contrast identifies scar formation and is routinely used to quantify infarct size (40). Repeated fibrosis measurements during therapy may provide insight into reversal of fibrosis, but empirical evidence of these approaches is limited. MR imaging with gadolinium-elastin may interrogate extracellular matrix generation with a higher predictive value than late gadolinium enhancement alone (87). Novel molecular imaging radiotracers also target active fibrosis. Imaging of fibroblast activation protein, highly expressed by myofibroblasts during transdifferentiation, demonstrated enrichment in the

border zone after MI in mice (88), which may allow monitoring of scar expansion and response to therapy. Although antifibrosis therapies have not entered clinical practice, chimeric T cell-mediated immunotherapy has shown promise to mitigate interstitial fibrosis in a mouse model of heart disease (89).

These targets and others may emerge for image-guided reparative therapy in the heart, if their transient signaling patterns are well characterized and matched tracer-therapeutic agent pairs become available.

THE NEXT STEPS: TRANSLATION AND BEYOND

DRUG DEVELOPMENT AND CLINICAL TRIALS. Molecular imaging contributed to understanding the benefits of progenitor cell therapy after MI, providing credence to the concept of low engraftment, poor retention, and limited differentiation of transplanted cells (46). Accordingly, therapeutic approaches have evolved to enhance paracrine effects at the site of injury and promote endogenous repair mechanisms. The development of new drugs targeting repair may be aided by growth and expansion of molecular imaging, both by direct labeling of therapeutic agents and longitudinal monitoring of the drug target and functional response. It is reasonable that further improvement of long-term outcome requires improved characterization of heterogeneity among the population of patients with MI to define those who would benefit from a specific therapy. Although the ultimate endpoint of clinical trials is necessarily survival, the identification of surrogate image-based endpoints may allow earlier indication of therapeutic efficacy and streamlined drug development. Beyond the use of imaging as an endpoint after therapy, or as a guide during therapy, the preferable use is to identify patients for response prior to therapy onset. The harmonization of therapeutic and imaging targets would allow such precision, reduce costs, and increase the likelihood of clinical trial success.

A SYSTEMS-BASED APPROACH FOR REPAIR. MI is increasingly recognized as a systemic disorder, with widespread consequences for other body regions and organs beyond tissue perfusion. The immune system is central to this interaction. MI is associated with increased hematopoietic organ activity (64), accelerates atherosclerosis and elevates plaque burden (90), increases the risk for subsequent infarction (91), and is associated with neuroinflammation (73), which may be related to cognitive decline (**Figure 4**). Total-body PET imaging bears intriguing possibilities to dissect these interactive networks between body systems, contributing to holistic therapeutic approaches to support repair. Ideally, future personalized therapy will then not only focus on restoring heart function but also include algorithms to identify and modulate risk emerging from potential jeopardy of networking organs throughout the body.

HIGHLIGHTS

- Novel cardiovascular therapies increasingly modify molecular targets that may be heterogeneously expressed by patients.
- Molecular imaging provides tissue-level information on target expression and drug delivery to guide therapeutic intervention.
- Implementing molecular imaging approaches may stratify patient risk and optimize therapeutic delivery to enhance repair.

CONCLUSIONS

As reparative therapy has evolved, molecular imaging to gauge cardiac repair must also adapt. Although conventional imaging tests provide added value for predicting outcome and determining therapeutic success, new approaches to monitor therapy at the time of intervention or during intervention by direct labeling or common targets offer new opportunities to evaluate myocardial repair. As exemplified with inflammation, this coupling of imaging and therapeutic target can provide insights into pathogenesis, evaluate drug efficacy, predict patient response, and guide precision therapy.

AUTHOR RELATIONSHIP WITH INDUSTRY

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