Am J Nucl Med Mol Imaging 2026;16(2):77-89
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0168880

Review Article

Positron emission tomography imaging of T-cell activity in cardiovascular disease and its emerging role in imaging adaptive immunity

Albab S Uddin[1], Shreyas Bulusu[1], Oluwaseyi M Oderinde[2,3], Qi-Huang Zheng[1]

[1]Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA; [2]Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, IN, USA; [3]Advanced Molecular Imaging Research Laboratory, Purdue University, West Lafayette, IN, USA

Received September 18, 2025; Accepted March 8, 2026; Epub April 15, 2026; Published April 30, 2026

Abstract: T lymphocytes are central mediators of cardiovascular disease, driving myocardial injury in myocarditis, transplant rejection, post-infarct remodeling, atherosclerosis, and post-viral syndromes. Yet current imaging tools ([^{18}F]FDG PET, somatostatin receptor tracers, CXCR4 PET, and cardiac MRI) offer only indirect or nonspecific measures of immune activity. The ability to noninvasively visualize and quantify T-cell infiltration and activation could transform diagnosis and management in cardio-immunology. Advances in immuno-PET have produced a growing arsenal of T-cell specific tracers. CD8-targeted agents (^{89}Zr-Df-IAB22M2C) and small-molecule probes such as [^{18}F]F-AraG have entered early clinical trials, demonstrating feasibility and safety in humans. Other tracers, including CD4- and CD3-directed antibodies, IL-2R and OX40 probes, checkpoint tracers (PD-1, CTLA-4), and granzyme B ligands, remain largely preclinical but show strong potential for cardiovascular translation. Applications span acute myocarditis, noninvasive transplant rejection surveillance, assessment of post-MI immune remodeling, plaque vulnerability in atherosclerosis, and systemic immune activation in long COVID. Compared with existing imaging modalities, T-cell PET offers cell-type specificity, quantitative longitudinal monitoring, and the capacity for whole-body immune mapping, particularly when integrated with total-body PET or hybrid PET/MR. Challenges include low T-cell density in the myocardium, tracer specificity, radiation burden, and the need for histopathologic validation. Future directions involve repurposing oncology tracers for cardiology, engineering antibody fragments with improved kinetics, and establishing T-cell PET as a mechanistic biomarker in cardiovascular clinical trials. With further innovation and validation, T-cell PET has the potential to evolve from an experimental tool into a clinically actionable modality, reshaping the management of immune-mediated heart disease.

Keywords: Positron emission tomography (PET), T-cell, tracer, cardiovascular disease, adaptive immunity, cardio-immunology

Introduction

Cardiovascular diseases remain the leading cause of death worldwide, and there is growing recognition that adaptive immunity, particularly with T lymphocytes, plays a central role in pathogenesis. Cytotoxic CD8^{+} T-cells, helper CD4^{+} subsets, and regulatory T-cells contribute to myocarditis, transplant rejection, ischemic remodeling, and atherosclerosis by driving inflammation, tissue injury, and maladaptive repair. In myocarditis, lymphocytic infiltration directly mediates myocyte damage. In transplantation, T-cells are the primary effectors of acute cellular rejection. After myocardial infarction, T-cells shape both clearance of necrotic debris and longer-term remodeling. In atherosclerosis, T-cell activation within plaques influences stability and clinical outcomes [1, 2].

Despite this biological importance, noninvasive imaging of T-cells remains limited. [^{18}F]FDG ([^{18}F]Fluorodeoxyglucose) PET (positron emission tomography) is widely used for cardiac sarcoidosis and inflammatory cardiomyopathy, but its uptake reflects a mixture of cardiomyocytes and innate immune cells and requires strict suppression protocols to reduce background noise, with variable reproducibility across centers. Cardiac MRI (magnetic resonance imaging) is invaluable for detecting edema and fibrosis but cannot distinguish immune cell subsets. Thus, current tools provide indirect or nonspecific markers of inflammation rather than direct visualization of adaptive immune activity [3].

Recent advances in immuno-PET now provide a framework to close this gap. Novel tracers have been developed to visualize specific T-cell populations or activation pathways, many of them first tested in oncology. Among the most advanced is the anti-CD8 minibody ^{89}Zr-Df-IAB22M2C, which demonstrated safety and CD8-rich tissue targeting in a first-in-human trial [4]. Small-molecule tracers such as [^{18}F]F-AraG (2'-Deoxy-2'-^{18}F-fluoro-9-β-D-arabinofuranosylguanine), which accumulates in activated T-cells, have also shown feasibility in early human studies [5]. These agents offer the possibility of cell-type-specific, quantitative, and longitudinal imaging of adaptive immunity in the heart.

This review highlights the emerging landscape of T-cell PET tracers in cardiovascular disease. We will outline the biologic rationale, survey tracer classes, summarize preclinical and early clinical findings, and discuss opportuni-

https://doi.org/10.62347/HDTI2868

ties and challenges in translating these tools to patient care.

This article is a narrative review of emerging T-cell-targeted PET tracers with relevance to cardiovascular disease. A focused literature search was conducted using the PubMed database, using combinations of keywords including "T-cell PET", "CD3 PET", "CD4 PET", "CD8 PET", "IL-2 receptor imaging", "OX40 imaging", "granzyme B PET", "$[^{18}F]$F-AraG", "myocarditis", "cardiac transplant rejection", "myocardial infarction", "atherosclerosis", and "long COVID". Priority was given to human studies when available, supplemented by preclinical cardiovascular and oncology literature where relevant to translational development. Additional references were identified through citation tracking of key publications.

Relevance of T-cells in cardiovascular disease

Myocarditis and inflammatory cardiomyopathies

Myocarditis is among the clearest examples of T-cell-driven cardiac injury. Biopsy specimens consistently demonstrate infiltration by both $CD4^+$ helper and $CD8^+$ cytotoxic T-cells, alongside macrophages and B cells. $CD8^+$ T-cells mediate direct myocyte lysis, while $CD4^+$ subsets orchestrate cytokine signaling that amplifies inflammation and fibrosis. Immune checkpoint inhibitor (ICI)-associated myocarditis, an increasingly recognized complication of cancer immunotherapy, further underscores the pathogenic role of T-cells: enhanced activation of $CD8^+$ lymphocytes has been observed in both experimental models and patient tissues [1, 6]. The degree of T-cell infiltration correlates with disease severity, yet current imaging cannot directly quantify these populations.

Cardiac transplant rejection

In heart transplantation, T-cells are the dominant effectors of acute cellular rejection. Alloantigen recognition drives clonal expansion and infiltration of $CD8^+$ and $CD4^+$ T-cells, which damage the allograft through cytotoxicity and cytokine release. Surveillance remains biopsy-dependent, and sampling error and procedural risks limit its utility. Molecular imaging of T-cells could provide a noninvasive, whole-organ assessment of rejection activity. Preclinical studies in mice have already demonstrated the feasibility of imaging graft-infiltrating T-cells with PET tracers [7], while reviews highlight the role of memory and effector T-cells as key mediators of rejection, noting that memory T-cells resist standard immunosuppression [8].

Post-myocardial infarction remodeling

Following myocardial infarction (MI), adaptive immunity contributes to the balance between repair and maladaptive remodeling. Early infiltration by $CD4^+$ and $CD8^+$ T-cells promotes clearance of necrotic debris, but persistent or excessive activation can impair healing and drive ventricular dilation. Regulatory T-cells (Tregs) play a protective role by restraining excessive inflammation and promoting resolution. In murine MI models, $CD4^+$ T-cell activation improved survival and wound healing [9], while $Foxp3^+$ Tregs limited adverse remodeling and improved functional recovery [10]. These data underscore the importance of adaptive immunity in repair and suggest that noninvasive imaging could help stratify post-MI patients at risk for heart failure, a population where current clinical risk models remain imperfect.

Atherosclerosis and plaque inflammation

Atherosclerosis is now understood as a chronic inflammatory condition. T-cells accumulate within plaques, where they regulate macrophage activation and smooth muscle cell behavior. $CD4^+$ effector subsets (Th1, Th17) secrete pro-atherogenic cytokines, while Tregs are protective. $CD8^+$ T-cells also contribute to plaque destabilization through cytotoxic activity. A landmark review summarized the diverse contributions of T-cell subsets in plaque progression and rupture risk [2]. More recently, single-cell sequencing has revealed exhausted and activated states of plaque-resident T-cells, populations that may represent both markers of vulnerability and therapeutic targets [11]. Imaging these subsets could refine cardiovascular risk prediction beyond what is currently possible with $[^{18}F]$FDG PET or CXCR4 PET.

Post-viral syndromes and long COVID

Persistent immune activation has been implicated in cardiac sequelae following viral infections, including COVID-19. Activated T-cells have been detected in myocardium and vascular tissues of patients with long COVID, raising concern for ongoing immune-mediated injury. Total-body PET with $[^{18}F]$F-AraG is being investigated as a tool to map systemic T-cell activation in this population. Total-body $[^{18}F]$F-AraG PET has demonstrated feasibility for systemic kinetic modeling in humans, providing a framework for investigating diffuse post-viral immune activation [12].

Across conditions like myocarditis, transplantation, MI, atherosclerosis, and viral sequelae, T-cells are central mediators of cardiac injury and repair. Their dynamic and disease-specific roles make them attractive imaging targets, yet no current modality can noninvasively quantify T-cell infiltration or activation in the heart. This unmet need provides the rationale for developing and translating T-cell PET tracers into cardiovascular medicine.

Classes of T-cell PET tracers with cardiac potential

T-cell-targeted PET tracers can be broadly categorized according to the biological feature they interrogate. Lineage markers such as CD3, CD4, and CD8 detect the presence and trafficking of total or subset-specific T-cells. Activation-associated targets, including the interleukin-2 receptor (IL-2R) and OX40, reflect recent immune activation. Immune checkpoint-related tracers targeting PD-1 or CTLA-4 provide insight into regulatory and exhaustion pathways that are particularly well characterized in oncology. Effector-function imaging, exemplified by granzyme B-directed tracers, aims to capture cytotoxic activity. Finally, metabolic tracers such as [^{18}F]F-AraG assess activated T-cell-specific metabolic pathways rather than surface phenotype. This framework highlights the complementary information provided by lineage, activation, regulatory, and functional imaging approaches.

General T-cell markers

CD8-targeted tracers: The most clinically advanced T-cell PET agent is the anti-CD8 minibody ^{89}Zr-Df-IAB22M2C. Human studies of CD8-targeted PET tracers have primarily been conducted in oncology, where safety, biodistribution, and tumor-infiltrating T-cell visualization have been demonstrated. Cardiovascular applications remain largely preclinical, with limited early translational data evaluating myocardial or vascular inflammation. In a first-in-human study, this tracer demonstrated safety, favorable dosimetry, and specific uptake in CD8-rich tissues and tumor lesions [4]. Subsequent work confirmed feasibility of imaging tumor-infiltrating CD8$^+$ T-cells in patients receiving immunotherapy [13]. More recently, Schwenck et al. extended these findings to metastatic cancer patients, providing robust human data on biodistribution [14]. These studies form the translational basis for applying CD8 imaging to myocarditis and transplant rejection.

CD4-targeted tracers: For CD4$^+$ helper T-cells, the ^{89}Zr-malDFO-GK1.5 cys-diabody has been tested preclinically. Tavaré and colleagues used this tracer to image T-cell reconstitution in mice following stem-cell transplantation [15], while Freise et al. explored how protein dosing influenced both imaging performance and T-cell function, showing that higher doses of the anti-CD4 cys-diabody could partially impair T-cell proliferation [16]. These results demonstrate preclinical feasibility but also highlight safety concerns that have limited clinical translation.

CD3-targeted tracers: Pan-T-cell imaging has been achieved with radiolabeled anti-CD3 antibodies. Beckford Vera et al. developed ^{89}Zr-DFO-anti-CD3, enabling visualization of total T-cell infiltration in tumors [17]. While less specific than CD4- or CD8-directed probes, this strategy could prove useful for global T-cell monitoring in transplant rejection.

It is important to note that lineage-directed tracers such as CD3, CD4, and CD8 primarily reflect T-cell presence and trafficking rather than functional state. Detection of CD8$^+$ T-cell infiltration does not necessarily indicate active cytotoxicity, nor does CD4 imaging distinguish between pathogenic effector subsets and regulatory T cells. As a result, lineage imaging alone may be insufficient to determine whether T-cell infiltration represents protective immunity, immune surveillance, or pathogenic inflammation. Complementary approaches targeting activation markers or effector molecules may therefore provide additional mechanistic insight.

Activation-specific tracers

IL-2/IL-2R (CD25): Interleukin-2 receptor α (CD25) is expressed on activated T-cells. Clinical experience with IL-2-based tracers has been reported predominantly in oncology and autoimmune contexts. Dedicated cardiovascular applications are more limited and remain largely investigational. Early tracer work with [^{18}F]FB-IL-2 demonstrated successful radiolabeling and in vivo uptake in activated T-cell populations [18]. More recent refinements have produced GMP-compliant tracers suitable for human translation [19, 20]. These studies highlight IL-2 PET as a promising approach for imaging acute T-cell activation in myocarditis or transplant rejection, and these early pilot human studies in oncology and autoimmunity further support its translational potential.

OX40 (CD134): OX40 is a costimulatory receptor transiently expressed on activated T-cells. Nobashi et al. demonstrated that ^{89}Zr-DFO-OX40 mAb could track vaccine-induced immune activation and glioblastoma responses in mice [21]. This biology suggests possible application to autoimmune myocarditis, where activated T-cell populations are central. Broader reviews have also highlighted OX40 imaging as an emerging precision immuno-PET strategy [22].

Immune checkpoint-directed tracers

Programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1): Checkpoint imaging has progressed rapidly. In a landmark study, Niemeijer et al. performed first-in-human PET with ^{18}F-BMS-986192 (PD-L1) and ^{89}Zr-nivolumab (PD-1), showing uptake in tumors and lymphoid tissues in patients with non-small cell lung cancer (NSCLC) [23]. Further work extended this approach to ^{89}Zr-pembrolizumab [24], while Miedema et al. reviewed applications across multiple checkpoint inhibitors, including nivolumab, pembrolizumab, durvalumab, and ipilimumab [25]. These data provide a framework for exploring PD-1 imaging in chronic cardiac inflammation and for detecting pathogenic PD-1+ T-cells in ICI-myocarditis.

CTLA-4: CTLA-4 is an inhibitory receptor expressed on activated T-cells that downregulates immune responses by competing with CD28 for binding to CD80/86. Ehlerding et al. reported preclinical immuno-PET of CTLA-4 using ^{64}Cu-DOTA-ipilimumab, successfully visualizing CTLA-4$^+$ T-cells in mouse tumor models [26]. Follow-up work with antibody fragments confirmed feasibility and altered tracer kinetics [27]. Although clinical translation has not yet occurred, CTLA-4 tracers could prove informative in

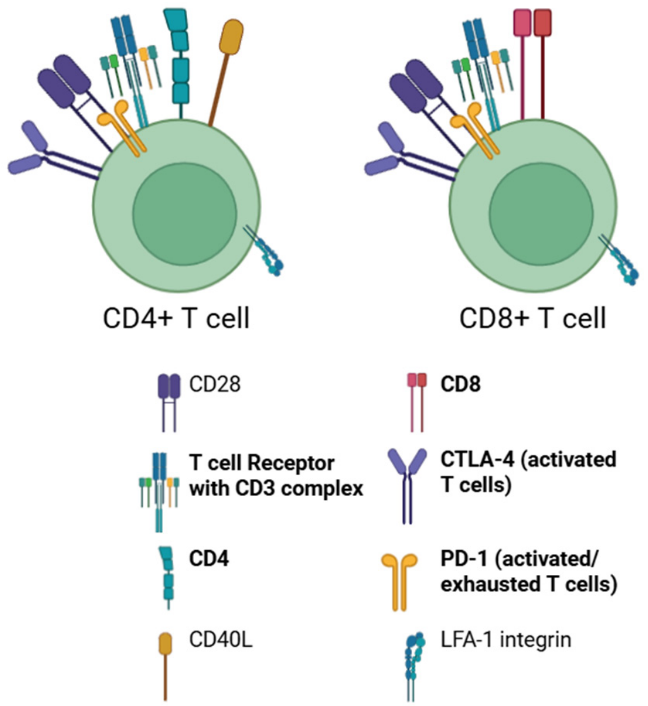


Figure 1. Key surface markers on CD4$^+$ and CD8$^+$ T-cells relevant to cardiovascular imaging. PET tracers have been developed for CD3, CD4, CD8, PD-1, and CTLA-4 (bolded). Other molecules such as CD28, CD40L, and LFA-1 are critical for T-cell biology but not yet directly targeted for imaging.

immune checkpoint inhibitor-related myocarditis and in chronic T-cell-mediated cardiac inflammation.

Functional and metabolism-based tracers

[^{18}F]F-AraG: [^{18}F]F-AraG is a guanosine analog retained in activated T-cells through mitochondrial nucleotide salvage pathways. Human studies of [^{18}F]F-AraG have primarily been conducted in oncology and immune-mediated diseases, demonstrating selective uptake in activated T-cells. Cardiovascular applications remain exploratory, with limited direct human cardiac data. It has demonstrated utility in preclinical oncology and immunotherapy response studies [28], and progressed into human imaging, showing safety and biodistribution in healthy volunteers and cancer patients [29, 30]. Total-body PET studies have established both biodistribution and quantitative kinetic parameters of [^{18}F]F-AraG in humans, supporting its use for whole-body immune monitoring [12]. Importantly, preclinical cardiac work has shown uptake in injured cardiomyocytes after ischemia-reperfusion, suggesting caution when interpreting myocardial signals [5].

Granzyme B tracers: Granzyme B is secreted by activated CD8$^+$ T-cells and NK cells during cytotoxic responses. Granzyme B-directed PET imaging has shown feasibility in human oncology studies as a marker of cytotoxic activity. In cardiovascular disease, evidence is currently restricted to preclinical models, and human validation remains to be established. Larimer et al. pioneered a peptide-based granzyme B tracer (^{68}Ga-GZP) that predicted immunotherapy response in mice [31]. LaSalle et al. extended this work to models of tumor reactivity [32], and Napier et al. confirmed its translational promise [33]. More recently, Shen et al. reported first-in-human evaluation of a novel "grazytracer" in patients, marking an important step toward clinical application [34].

Together, these tracers represent a pipeline for imaging T-cells at multiple stages: presence (CD3, CD4, CD8), activation (IL-2R, OX40), dysfunction (PD-1, CTLA-4), and effector function ([^{18}F]F-AraG, granzyme B). While most have been developed in oncology, their mechanisms directly align with the immune pathways central to myocarditis, transplant rejection, and ischemic remodeling. This growing toolkit provides a strong rationale for advancing T-cell PET into cardiovascular imaging.

The key surface markers on CD4$^+$ and CD8$^+$ T-cells relevant to cardiovascular imaging are shown in **Figure 1**. A schematic overview of T-cell PET tracers for cardiovascular imaging applications is shown in **Figure 2**. An overview of PET heart tracers is listed in **Table 1**.

Cardiovascular imaging applications of T-cell PET

Although several T-cell-targeted PET tracers have progressed to human evaluation in oncology, cardiovascular applications remain comparatively early in development. Most cardiac and vascular data are derived from preclinical models, with limited dedicated human cardiovascular studies to date.

T-cell PET for myocarditis and inflammatory cardiomyopathies

Myocarditis, whether viral, autoimmune, or related to ICIs, is characterized by T-cell-driven myocyte injury. Histology consistently reveals CD8$^+$ cytotoxic and CD4$^+$ helper T-cell infiltration, often with associated fibrosis. The severity of infiltration correlates with clinical outcomes [1]. ICI-associated myocarditis, though uncommon, carries high mortality, and is primarily mediated by activated CD8$^+$ T-cells [6].

Molecular imaging could improve diagnosis and monitoring. [^{18}F]FDG PET is already used in myocarditis and sarcoidosis, but its uptake reflects both myocytes and innate immune cells, and suppression protocols are imperfect [3]. T-cell tracers may provide more specific readouts: (1) CD8 tracers (^{89}Zr-IAB22M2C) could quantify cytotoxic infiltrates. (2) IL-2R tracers (^{18}F-FB-IL-2) might highlight activated T-cells in acute flares. (3) [^{18}F]F-AraG, though promising, requires caution due to uptake in injured cardiomyocytes [5]. (4) OX40 tracers may eventually identify activated autoreactive T-cells in autoimmune myocarditis. Because it is transiently expressed during activation, it may allow temporal mapping of acute immune flares in myocarditis [21].

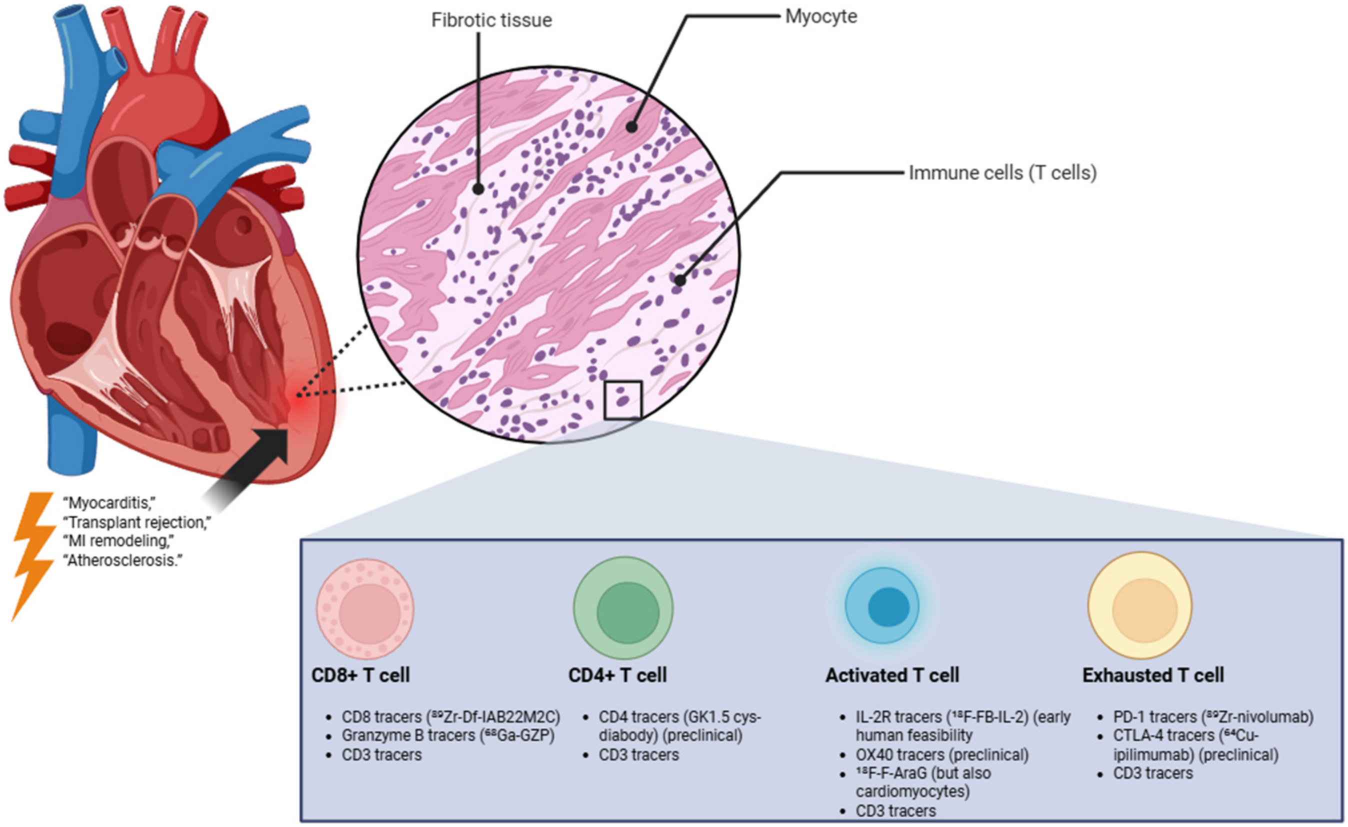


Figure 2. Schematic overview of T-cell PET tracers for cardiovascular imaging applications. The heart and myocardial section highlight immune cell infiltration in myocarditis, transplant rejection, post-MI remodeling, and atherosclerosis. Tracers target different T-cell states: CD8 tracers (^{89}Zr-IAB22M2C; clinical), CD4 tracers (GK1.5 cys-diabody; preclinical), activation tracers (^{18}F-FB-IL-2; early human feasibility; OX40; preclinical; [^{18}F]F-AraG; clinical but also labels myocytes), and checkpoint tracers (PD-1: ^{89}Zr-nivolumab; clinical; CTLA-4: ^{64}Cu-ipilimumab; preclinical). This framework shows the spectrum of tools being translated from oncology to cardiovascular immunology.

Together, these tools could complement MRI-based Lake Louise criteria (standard for diagnosing myocarditis) by directly visualizing immune subsets, enabling more precise monitoring of therapy response.

Clinically, T-cell PET could assist in distinguishing active immune-mediated myocarditis from residual scar or non-inflammatory cardiomyopathy, potentially informing decisions regarding initiation, escalation, or tapering of immunosuppressive therapy. It may also help guide biopsy targeting in selected cases.

T-cell PET for cardiac transplant rejection

T-cell-mediated rejection remains the leading cause of early morbidity after heart transplantation. Current surveillance relies on endomyocardial biopsy, which is invasive and prone to sampling errors. Noninvasive imaging of T-cell infiltration offers a potential paradigm shift.

Preclinical work has demonstrated feasibility. Hirai et al. showed PET detection of graft-infiltrating T-cells in a murine transplant model, with signal preceding histologic rejection [7]. An interesting review has highlighted that both effector and memory T-cells orchestrate rejection [8].

Translation of tracers into this space is compelling: (1) CD8 tracers (^{89}Zr-IAB22M2C) could detect cytotoxic infiltrates driving acute rejection. (2) IL-2R tracers may capture activated effector cells during early rejection. (3) Checkpoint tracers (PD-1/CTLA-4) might identify regulatory versus exhausted phenotypes relevant to chronic rejection or tolerance.

A noninvasive T-cell PET assay could reduce biopsy frequency and provide whole-organ immune surveillance, while complementary tools would still be needed to assess antibody-mediated rejection.

In the transplant setting, T-cell PET could enable earlier detection of cellular rejection and reduce reliance on routine endomyocardial biopsy, particularly for surveillance in asymptomatic patients. Quantitative monitoring may also help guide immunosuppressive adjustments and assess treatment response.

T-cell PET for myocardial infarction and post-infarction remodeling

Adaptive immunity is increasingly recognized as a determinant of healing after MI. Experimental depletion of CD4^{+} or CD8^{+} T-cells alters scar composition, ventricular

Table 1. Overview of PET tracers targeting T-cells, their molecular targets, isotopes, stage of development, and potential applications in cardiovascular disease*

Tracer/Example	Target	Isotope	Development stage	Primary clinical use	Potential cardiac application	Key references
^{89}Zr-Df-IAB22M2C (minibody)	CD8	^{89}Zr	Clinical (cancer patients; multiple trials)	Imaging CD8^{+} tumor-infiltrating lymphocytes	Myocarditis, transplant rejection	[4, 13, 14]
^{89}Zr-malDFO-GK1.5 cDb	CD4	^{89}Zr	Preclinical (murine transplant, inflammation)	Imaging helper T-cell subsets	Myocarditis, post-MI repair	[15, 16]
^{89}Zr-DFO-anti-CD3	CD3 (pan-T-cell)	^{89}Zr	Preclinical	Broad T-cell imaging	Global infiltration in myocarditis, rejection	[17]
[^{18}F]FB-IL-2	IL-2R (CD25)	^{18}F	Early clinical (pilot human studies)	Activated T-cell imaging in oncology/autoimmunity	Acute myocarditis, rejection	[18, 19]
^{89}Zr-DFO-OX40 mAb	OX40 (CD134)	^{89}Zr	Preclinical (cancer, vaccination models)	Activated T-cell responses	Autoimmune myocarditis, graft rejection	[21]
^{89}Zr-nivolumab/ ^{89}Zr-pembrolizumab	PD-1	^{89}Zr	Clinical (oncology trials)	Exhausted/activated T-cell imaging under ICI therapy	Chronic cardiac inflammation, ICI-myocarditis	[23, 24]
^{64}Cu-DOTA-ipilimumab	CTLA-4	^{64}Cu	Preclinical (murine tumors)	Checkpoint expression imaging	ICI-related myocarditis (experimental)	[26]
[^{18}F]F-AraG	Activated T-cells (dGK pathway)	^{18}F	Clinical (human dosimetry, cancer/viral studies)	Imaging activated T-cells	Myocarditis, MI remodeling (note: myocyte uptake), long COVID	[5, 12, 30]
^{68}Ga-GZP (granzyme B peptide)	Granzyme B (cytotoxic effector)	^{68}Ga	Early clinical (first-in-human; mostly preclinical)	Predicting immunotherapy response	Cytotoxicity in myocarditis, post-MI injury	[31, 32, 34]

*Tracers are categorized by T-cell subset or functional state. Most agents are translated from oncology; those noted as "clinical" or "early clinical" have entered human studies, whereas "preclinical" remain in animal models. Potential cardiac applications include myocarditis, transplant rejection, MI remodeling, atherosclerosis, and post-viral syndromes such as long COVID.

dilation, and survival. CD4^{+} T-cell activation improves wound healing [9], while regulatory T-cells restrain excessive inflammation and limit adverse remodeling [10].

T-cell PET could provide new biomarkers for post-MI risk stratification: (1) [^{18}F]F-AraG has already been tested in ischemia-reperfusion models, where it accumulated in both activated T-cells and injured myocytes [5]. (2) Granzyme B tracers could monitor CD8^{+} cytotoxic activity during early tissue injury [32]. (3) IL-2R tracers might visualize T-cell activation during the inflammatory-repair transition phase.

By mapping adaptive immune dynamics, these tracers could identify patients at risk of adverse remodeling and guide timing of immunomodulatory therapies.

In post-MI remodeling, visualization of T-cell subsets may help stratify patients at risk for adverse ventricular remodeling and inform consideration of targeted immunomodulatory strategies in clinical trials.

T-cell PET for atherosclerosis and plaque inflammation

Atherosclerosis is now understood as a chronic inflammatory disease with strong T-cell involvement. CD4^{+} Th1 and Th17 cells promote inflammation, while regulatory T-cells are protective. CD8^{+} T-cells contribute to plaque destabilization through cytotoxicity. Single-cell analyses of human plaques have revealed exhausted and activated T-cell subsets that shape plaque vulnerability [2, 11].

Current plaque imaging relies heavily on [^{18}F]FDG and ^{68}Ga-Pentixafor (CXCR4), which primarily reflect macrophage activity. T-cell tracers offer the possibility of subset-specific plaque imaging, particularly: (1) CD4/CD8 tracers to quantify effector subsets. (2) Checkpoint tracers (PD-1, CTLA-4) to assess exhaustion and regulation. (3) IL-2 tracers for plaque-associated activated T-cells. This could refine risk prediction beyond standard imaging by directly measuring the immune subsets most responsible for destabilization.

In atherosclerosis, T-cell-specific imaging may refine identification of high-risk plaques characterized by adaptive immune activation and potentially guide selection of anti-inflammatory or immune-modifying therapies.

T-cell PET for post-viral syndromes and long COVID

Post-viral syndromes such as long COVID frequently include cardiovascular manifestations, including myocarditis-like injury, dysautonomia, and microvascular dysfunction. Persistent immune activation, including activated T-cells, has been implicated in these syndromes.

As previously mentioned, [^{18}F]F-AraG PET has emerged as a practical tool for systemic T-cell imaging [12]. In post-viral syndromes such as long COVID, it could stratify patients by degree of systemic versus cardiac involvement, clarify mechanisms of persistent inflammation, and guide the development or monitoring of targeted immunomodulatory therapies.

In post-viral syndromes including long COVID, T-cell PET remains exploratory but may help clarify whether persistent cardiac symptoms are associated with ongoing ad-

Table 2. Cardiovascular imaging applications of T-cell PET*

Disease Context	Pathophysiology	Key T-cell Subsets	Current Imaging Limitations	Candidate T-cell PET Tracers	Key References
Myocarditis (viral, autoimmune, ICI-associated)	T-cell-driven myocyte injury; CD8$^+$ cytotoxic cells dominate; CD4$^+$ helper cells and Tregs modulate severity	CD8$^+$, CD4$^+$, Tregs, activated T-cells	^{18}F-FDG PET nonspecific; CMR detects edema/fibrosis but not immune subsets	CD8 tracers (^{89}Zr-IAB22M2C), IL-2R (^{18}F-FB-IL-2), OX40, [^{18}F]F-AraG (with cardiomyocyte uptake caveat)	[5, 6]
Cardiac transplant rejection	T-cell-mediated cytotoxicity drives acute cellular rejection; memory T-cells involved in chronic rejection	CD8$^+$, CD4$^+$, activated/memory T-cells	Surveillance biopsies are invasive and prone to sampling error	CD8 tracers, IL-2R tracers, checkpoint tracers (PD-1, CTLA-4)	[7, 8]
Myocardial infarction & remodeling	T-cells influence post-MI healing, scar formation, and adverse remodeling; Tregs protective	CD4$^+$, CD8$^+$, Tregs	CMR detects scar/edema but cannot quantify immune subsets	[^{18}F]F-AraG, IL-2R tracers, Granzyme B tracers (^{68}Ga-GZP)	[9, 10, 31]
Atherosclerosis & plaque instability	T-cells drive plaque inflammation and instability; Th1/Th17 promote, Tregs suppress	CD4$^+$, CD8$^+$, Tregs, exhausted T-cells	^{18}F-FDG and CXCR4 PET reflect macrophage activity; cannot resolve T-cell subsets	CD4/CD8 tracers, IL-2R, PD-1 tracers	[2, 11]
Post-viral syndromes (long COVID, others)	Persistent systemic immune activation; T-cell-mediated vascular/cardiac involvement suspected	Activated CD4$^+$/CD8$^+$ T-cells	CMR shows inflammation/fibrosis; no systemic immune imaging	[^{18}F]F-AraG with total-body PET for systemic mapping	[12]

*Key disease contexts include myocarditis, transplant rejection, myocardial infarction and remodeling, atherosclerosis, and post-viral syndromes. For each, the underlying pathophysiology, relevant T-cell subsets, and limitations of current imaging are summarized alongside candidate PET tracers and representative references.

aptive immune activation, thereby informing decisions regarding immunomodulatory treatment trials. Evidence is derived from small and heterogeneous cohorts. Persistent tracer uptake may reflect systemic immune activation rather than cardiac-specific inflammation, and careful interpretation within clinical context is essential. Dedicated cardiovascular validation studies will be required to determine the specificity and prognostic relevance of T-cell imaging in post-viral syndromes.

Across disease states, T-cell imaging provides a more precise lens on adaptive immunity in the heart and vasculature. Myocarditis and transplant rejection stand out as the most immediate clinical applications, given their reliance on T-cell-mediated injury and the limitations of current diagnostic approaches. Post-MI remodeling, atherosclerosis, and post-viral syndromes represent expanding frontiers where PET tracers could uncover new biology and identify therapeutic windows. The cardiovascular imaging applications of T-cell PET are listed in **Table 2**.

Technical and quantification considerations in cardiovascular T-cell PET

Across cardiovascular applications, accurate quantification of T-cell-targeted PET presents unique technical challenges. Although standard uptake values (SUV) are commonly reported, vascular and myocardial imaging frequently rely on target-to-background ratios (TBR) to account for circulating tracer activity and variable blood pool signal. In atherosclerotic plaque imaging, small lesion size renders measurements particularly susceptible to partial volume effects, potentially underestimating true tracer uptake. Moreover, variability in the selection of blood pool reference regions and vessel wall region-of-interest (ROI) definition may influence calculated TBR values and limit reproducibility across studies. Cardiac and respiratory motion further degrade spatial resolution and may introduce quantification variability, underscoring the importance of motion correction and standardized acquisition protocols. Spillovers from adjacent blood pool or nearby lymphoid structures may confound interpretation, especially in coronary and great vessel imaging. As T-cell PET moves toward cardiovascular translation, harmonized imaging protocols, careful ROI methodology, and validation against histopathology or clinically meaningful endpoints will be essential for reproducible and interpretable results.

Comparisons with existing imaging modalities

[^{18}F]FDG PET

[^{18}F]FDG PET is the most widely used molecular imaging tool for cardiac inflammation, particularly in sarcoidosis and myocarditis. It has high sensitivity but suffers from two major limitations: 1) physiologic myocardial uptake due to glucose metabolism, requiring dietary or heparin suppression protocols that are cumbersome, variably effective, and prone to false positives in patients with diabetes or obesity; and 2) lack of cellular specificity, as FDG accumulates in both activated macrophages and cardiomyocytes. While consensus guidelines from the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the American Society of Nuclear Cardiology (ASNC) support its role in cardiac sarcoidosis [3], the method remains an indirect readout of inflammation. T-cell tracers would provide specificity for adaptive immune processes, potentially complementing or even replacing FDG in myocarditis and transplant rejection.

Somatostatin receptor (SSTR) tracers

Radiolabeled somatostatin analogs such as ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC, widely used for neuroendocrine

Table 3. Comparison of macrophage-centric inflammation imaging and T-cell-targeted PET in cardiovascular disease*

Imaging Strategy	Primary Immune Target	Strengths	Key Limitations	What T-cell PET Adds
[^{18}F]FDG PET	Glucose metabolism in activated inflammatory cells (predominantly macrophages)	Widely available; high sensitivity; established clinical use	Low specificity; physiologic myocardial uptake requires suppression; cannot distinguish immune subsets	Cell-specific visualization of adaptive immunity and subset-specific tracking
SSTR-targeted PET (e.g., ^{68}Ga-DOTATATE)	Somatostatin receptor-expressing activated macrophages	Greater specificity for activated macrophages compared with FDG; useful in plaque imaging	Remains macrophage-focused; limited insight into adaptive immune contribution	Direct assessment of T-cell presence and activation within lesions
CXCR4-targeted PET	CXCR4-expressing inflammatory leukocytes	Reflects leukocyte recruitment and inflammatory signaling	Not specific to T cells; signal may reflect multiple immune cell types	Differentiation of innate versus adaptive immune components
T-cell–targeted PET (CD3, CD4, CD8, IL-2R, OX40, PD-1, CTLA-4, granzyme B, [^{18}F]F-AraG)	T-cell lineage, activation, checkpoint status, or cytotoxic function	Subset-specific and function-oriented imaging of adaptive immunity; potential for mechanistic phenotyping	Lower cellular abundance in myocardium; early-stage cardiovascular validation	Mechanistic characterization of T-cell-driven pathology and potential guidance of immunomodulatory therapy

*Although macrophage-centric tracers such as [^{18}F]FDG, SSTR-targeted agents, and CXCR4 imaging have advanced cardiovascular inflammation imaging, they primarily reflect innate immune activity. In contrast, T-cell-targeted PET provides direct insight into adaptive immune mechanisms.

tumors, also accumulate in inflammatory lesions. Their uptake reflects activated macrophages expressing somatostatin receptors. Early studies have demonstrated DOTATATE uptake in cardiac sarcoidosis and systemic inflammatory conditions [35]. However, these tracers are not specific to T-cells. They may serve as complementary tools for imaging macrophage-driven inflammation, but they cannot resolve adaptive immunity.

CXCR4 tracers

The chemokine receptor CXCR4 is expressed on monocytes, macrophages, and some lymphocytes. ^{68}Ga-pentixafor, a CXCR4-targeted PET tracer, has been applied to atherosclerosis and myocarditis. In patients with large-vessel vasculitis and atherosclerotic plaques, pentixafor PET demonstrated strong uptake in inflamed lesions [36, 37]. However, CXCR4 expression is not exclusive to T-cells, as it is also present on monocytes, macrophages, and hematopoietic precursors, leading to overlap with innate immune activation. Compared with emerging T-cell tracers, CXCR4 imaging offers broader inflammatory profiling but less specificity for adaptive lymphocytes.

Cardiac MRI

Cardiac MRI (CMR) is a cornerstone of noninvasive myocarditis and cardiomyopathy evaluation. The Lake Louise criteria rely on T2-weighted imaging for edema and late gadolinium enhancement (LGE) for fibrosis [38]. T1/T2 mapping has increased sensitivity for diffuse inflammation. However, MRI cannot distinguish immune subsets and provides only surrogate markers of injury (edema, scar). While MRI remains indispensable for structural and functional characterization, T-cell PET would add cell-specific resolution, enabling correlation between immune activity and tissue damage.

Integration and complementarity

Each modality has strengths and weaknesses: (1) [^{18}F]FDG PET: sensitive but nonspecific. (2) SSTR tracers: macrophage-specific, not adaptive. (3) CXCR4 PET: chemokine receptor-based, intermediate specificity. (4) CMR: excellent structural/functional resolution, no immune subset data.

T-cell PET offers complementary value by targeting adaptive immunity directly. Integration of T-cell tracers with total-body PET could provide systemic context, while hybrid PET/MR could merge structural information with immune profiling. This multimodal strategy may define the future of cardio-immunology imaging.

[^{18}F]FDG PET, SSTR tracers, CXCR4 imaging, and CMR have each advanced the field of cardiovascular inflammation imaging, but they remain nonspecific or indirect measures of adaptive immunity. T-cell PET tracers uniquely offer cell-type specificity, the potential to resolve immune heterogeneity, and quantitative tracking over time. Rather than replacing existing modalities, they are likely to serve as complementary tools, particularly when integrated with hybrid PET/MR or total-body PET platforms. This synergy could transform both research and clinical practice into cardio-immunology. A structured comparison of these different approaches is summarized in **Table 3**. Conventional cardiac PET imaging for perfusion assessment is shown in **Figure 3**, and a normal biodistribution of ^{68}Ga-DOTATATE PET (left) and ^{18}F-FDG PET (right) is shown in **Figure 4**.

Advantages and challenges/limitations of T-cell PET imaging

Advantages

Cell-type specificity: Unlike [^{18}F]FDG PET or ^{68}Ga-DOTATATE, which mainly reflect metabolism or macrophage activity, T-cell tracers directly bind to lineage markers such as CD3, CD4, and CD8, or activation molecules like IL-2R and PD-1. In first-in-human studies, the anti-CD8 minibody ^{89}Zr-Df-IAB22M2C demonstrated safe biodistri-

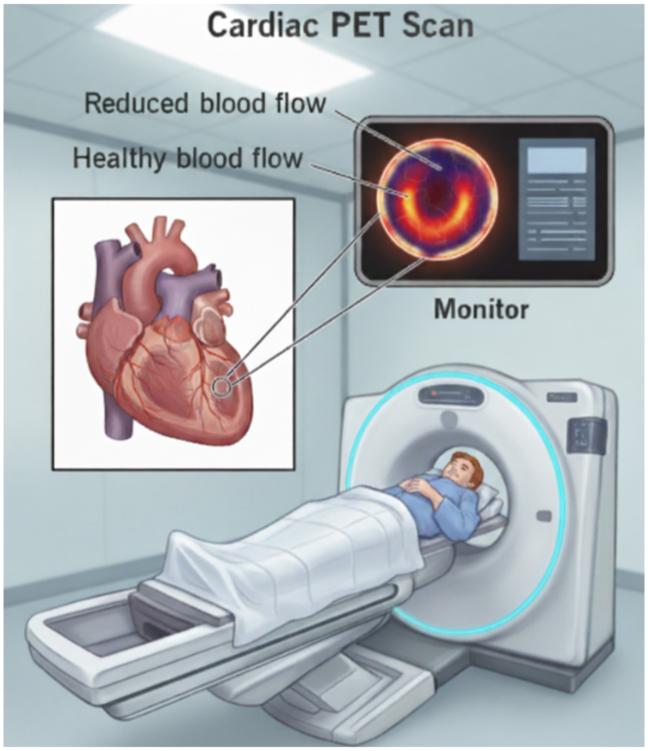


Figure 3. Conventional cardiac PET imaging for perfusion assessment. PET is widely used in cardiology to evaluate myocardial blood flow and perfusion defects, as illustrated by the distinction between regions of reduced and healthy blood flow. While established tracers such as ^{13}N-ammonia and ^{82}Rb provide robust perfusion imaging, they do not capture immune cell activity, underscoring the complementary role of novel T-cell-targeted tracers for evaluating inflammation.

bution and specific uptake in CD8-rich tissues, validating the principle of adaptive immune-specific imaging [4]. This approach was further extended by Farwell et al., who showed that CD8 PET could quantify tumor-infiltrating lymphocytes in patients with cancer, highlighting its potential for longitudinal monitoring [13].

Quantitative and longitudinal assessment: Because PET allows absolute quantification, tracer uptake can be followed over time. This provides a way to monitor immune dynamics, assess therapy response, and detect recurrence risk, particularly relevant in transplant rejection and ICI-associated myocarditis.

Whole-body systemic view: Total-body PET has enabled simultaneous imaging of cardiac and systemic immune activity. Total-body PET with [^{18}F]F-AraG has demonstrated dynamic imaging and kinetic modeling, showing how immune activation can be tracked systemically in real time [12].

Integration with multimodal imaging: T-cell PET can be combined with structural and functional imaging. Cardiac MRI, for example, remains the standard for detecting myocardial edema and fibrosis [38], but it cannot identify immune subsets. Hybrid PET/MR could merge tissue characterization with cell-specific immune imaging for a more complete picture.

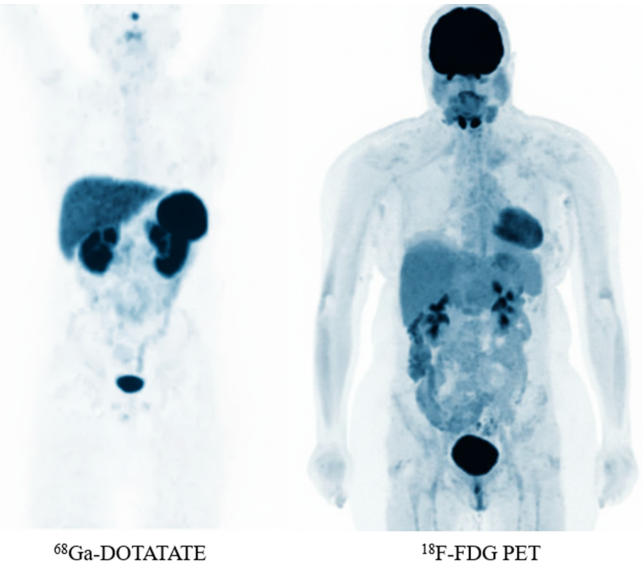


Figure 4. Normal biodistribution of ^{68}Ga-DOTATATE PET (left) and ^{18}F-FDG PET (right). DOTATATE shows physiologic uptake in the liver, spleen, kidneys, and bladder, reflecting somatostatin receptor expression in macrophages. In contrast, FDG demonstrates widespread uptake in the myocardium, brain, bowel, and skeletal muscle due to glucose metabolism. While both modalities are useful in cardiovascular inflammation imaging, neither provides T-cell specificity, underscoring the potential role for novel T-cell-targeted tracers.

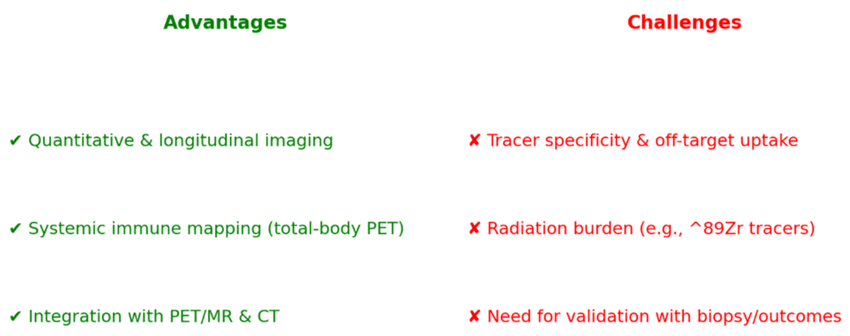
Challenges and limitations

Tracer specificity in the heart: Although [^{18}F]F-AraG is designed to label activated T-cells, it also shows uptake in stressed cardiomyocytes, as demonstrated in ischemia-reperfusion models [5]. This off-target binding complicates interpretation in cardiac injury.

Low T-cell density: Cardiac infiltrates are often sparse compared with tumors, lowering signal-to-noise ratios. Early preclinical work with pan-T-cell tracers such as ^{89}Zr-anti-CD3 demonstrated feasibility but also highlighted the difficulty of detecting low-abundance populations in vivo [17].

Dosimetry and safety: Antibody-based tracers labeled with ^{89}Zr provide high specificity but deliver higher radiation doses, which may limit their use in longitudinal cardiovascular imaging. Checkpoint tracers such as ^{64}Cu-DOTA-ipilimumab illustrate the trade-off between specificity and prolonged circulation times [26]. In contrast, small-molecule tracers like [^{18}F]F-AraG achieve lower radiation exposure, though safety and biodistribution data confirm systemic uptake that must be accounted for in clinical use [30].

Pharmacokinetics and background uptake: Antibody tracers often clear slowly and accumulate in blood and lym-



Advantages	Challenges
✔ Quantitative & longitudinal imaging	✘ Tracer specificity & off-target uptake
✔ Systemic immune mapping (total-body PET)	✘ Radiation burden (e.g., ^89Zr tracers)
✔ Integration with PET/MR & CT	✘ Need for validation with biopsy/outcomes

Figure 5. Advantages and challenges of T-cell PET imaging in cardiovascular disease. Advantages include cell-type specificity, quantitative longitudinal assessment, systemic immune mapping with total-body PET, and integration with multimodal imaging. Challenges include low T-cell density in the myocardium, tracer specificity and off-target uptake, radiation burden with long-lived isotopes, and the need for validation against biopsy and clinical outcomes.

phoid tissues. A recent review of checkpoint immuno-PET in humans confirmed high physiological uptake in spleen and lymph nodes, raising challenges for quantification in nearby cardiac tissue [25].

Validation requirements: To establish clinical value, PET findings must correlate with biopsy and outcomes. In myocarditis and transplant rejection, histology remains the reference standard but is invasive and limited by sampling error. Carefully designed trials that integrate imaging, pathology, and outcomes are critical to move the field forward.

Cost and accessibility: Specialized isotopes (^{89}Zr, ^{64}Cu) and radiochemistry expertise limit widespread adoption. Early implementation will likely remain confined to academic centers until streamlined production and distribution pathways are established.

T-cell PET offers unprecedented specificity and quantitative insight into adaptive immune activity in cardiovascular disease. Advantages include immune subset targeting, longitudinal monitoring, systemic imaging with total-body PET, and complementarity with MRI. Limitations include off-target uptake, low T-cell density in the heart, radiation burden, slow pharmacokinetics, and validation challenges. Addressing these barriers through tracer engineering, novel isotopes, and prospective clinical trials will determine whether T-cell PET evolves from an experimental tool to a clinical standard. Advantages and challenges of T-cell PET imaging in cardiovascular disease are summarized in **Figure 5**.

Future directions

Repurposing oncology tracers for cardiology

Most of the leading T-cell PET tracers were developed for oncology, where immune checkpoint inhibitors have driven the need to noninvasively track T-cell biology. CD8 tracers such as ^{89}Zr-Df-IAB22M2C have already demonstrated safety and biodistribution in cancer patients [4, 13]. Repurposing these agents for cardiovascular disease could accelerate translation, particularly since some tracers are already IND-cleared for oncology, streamlining regulatory and manufacturing hurdles. For example, trials of [^{18}F]F-AraG in oncology have established human safety profiles [30], enabling investigators to pivot toward myocarditis or transplant rejection studies without starting from scratch.

Engineering next-generation tracers

Despite early success, antibody-based tracers remain limited by slow kinetics and high radiation exposure. Future efforts are focusing on engineered fragments (cys-diabodies, minibodies, nanobodies) that balance specificity with faster clearance. For instance, preclinical work with anti-CD4 cys-diabodies achieved robust T-cell imaging in mouse models with improved pharmacokinetics compared to full antibodies [15]. Similar approaches may yield cardiovascular-optimized tracers that can resolve sparse T-cell infiltrates without excessive background uptake. Advances in click chemistry and site-specific labeling may also produce more consistent, high-affinity probes.

Multimodal imaging strategies

Standalone PET provides specificity but has limited structural resolution. Combining T-cell tracers with MRI could bridge this gap. CMR already excels at characterizing edema, fibrosis, and function [38], while PET adds immune-cell specificity. Integrated PET/MR platforms could simultaneously map immune activation and tissue remodeling, enhancing diagnostic precision in myocarditis and post-MI remodeling. Similarly, computed tomography (CT) angiography combined with T-cell PET may illuminate both plaque burden and immune activity in atherosclerosis.

Leveraging total-body PET

The emergence of total-body PET has expanded possibilities for systemic immune imaging. Because [^{18}F]F-AraG PET has been shown to track activated T-cells with high sensitivity across organ systems, it has great utility for studying widespread immune involvement [12]. Applying this technology to cardiovascular patients could reveal not only local myocardial infiltration but also systemic immune signatures. For example, it could help in distinguishing patients with isolated cardiac involvement from those with widespread immune activation in long COVID or sarcoidosis.

Clinical trial integration

Perhaps the most impactful role for T-cell PET will be as a biomarker in clinical trials. For myocarditis, imaging could stratify patients by T-cell burden and guide immunosuppressive therapy intensity. In transplantation, T-cell PET could reduce reliance on biopsies by providing whole-organ rejection surveillance. In MI and atherosclerosis, PET endpoints might help test immunomodulatory therapies aimed at reducing adverse remodeling or plaque instability. The ability to noninvasively quantify adaptive immune activity would provide trialists with a mechanistic and dynamic biomarker not available through traditional imaging.

Regulatory and practical considerations

For T-cell PET to become routine, regulatory approval and logistical scalability are essential. Small-molecule tracers like [^{18}F]F-AraG and ^{18}F-FB-IL-2 are more amenable to distribution across PET centers than ^{89}Zr-labeled antibodies, which require specialized production and longer half-lives. Efforts to simplify radiochemistry, standardize protocols, and harmonize quantification will be critical for adoption beyond academic hubs. Engagement with the FDA and EMA early in tracer development will help accelerate this process.

The future of T-cell PET in cardiology lies at the crossroads of tracer innovation, multimodal imaging, and clinical application. Repurposing oncology tracers offers a rapid translational pathway, while engineering next-generation agents may overcome pharmacokinetic barriers. Hybrid PET/MR and total-body PET promise richer biologic insights, and integration into clinical trials could establish T-cell imaging as a validated biomarker. If logistical and regulatory hurdles can be addressed, T-cell PET has the potential to redefine how we diagnose, monitor, and treat immune-mediated cardiovascular disease.

Concluding remarks

T-cell PET imaging represents an emerging frontier in cardiovascular medicine. By targeting lineage markers (CD3, CD4, CD8), activation molecules (IL-2R, OX40), checkpoints (PD-1, CTLA-4), and functional mediators (granzyme B, [^{18}F]F-AraG), these tracers provide a cell-specific window into adaptive immune activity. Their application to myocarditis, transplant rejection, myocardial infarction, atherosclerosis, and post-viral syndromes addresses a central unmet need: the ability to noninvasively visualize and quantify T-cell-driven pathology in the heart. Compared with existing modalities such as [^{18}F] FDG PET and cardiac MRI, T-cell PET offers greater specificity and the potential for quantitative longitudinal monitoring. Early clinical studies, especially with CD8 tracers and [^{18}F]F-AraG, demonstrate feasibility and safety, while preclinical work continues to expand the tracer pipeline. Importantly, much of the existing human clinical experience has been derived from oncology applications, and dedicated cardiovascular validation remains comparatively limited. Translation to cardiac and vascular disease will require focused studies to define diagnostic performance, prognostic value, and impact on clinical decision-making in cardiovascular populations. Integration with hybrid PET/MR and total-body PET further enhances its promise, enabling systemic immune mapping alongside cardiac tissue characterization. Challenges remain, including low T-cell density in the myocardium, off-target uptake, dosimetry concerns, and the need for rigorous clinical validation. Nonetheless, ongoing tracer engineering, repurposing of oncology-developed probes, and incorporation into clinical trials provide clear pathways forward. In summary, T-cell PET has the potential to transform cardio-immunology by uniting molecular specificity with noninvasive imaging. If current barriers are addressed, these tracers may evolve from experimental tools into clinically actionable biomarkers, reshaping the diagnosis and management of immune-mediated cardiovascular disease. Ultimately, the success of T-cell PET will depend on showing that immune imaging meaningfully alters clinical decision-making and outcomes, with rigorous biopsy-correlated and outcomes-driven validation serving as the critical next step.

Disclosure of conflict of interest

None.

Address correspondence to: Albab S Uddin and Dr. Qi-Huang Zheng, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 1345 West 16th Street, Room 206, Indianapolis, IN 46202, USA. E-mail: asuddin@iu.edu (ASU); qzheng@iu.edu (QHZ)

References

[1] Golino M, Harding D, Del Buono MG, Fanti S, Mohiddin S, Toldo S, Smyth J, Sanna T, Marelli-Berg F and Abbate A. Innate and adaptive immunity in acute myocarditis. Int J Cardiol 2024; 404: 131901.

[2] Wolf D and Ley K. Immunity and inflammation in atherosclerosis. Circ Res 2019; 124: 315-327.

[3] Chareonthaitawee P, Beanlands RS, Chen W, Dorbala S, Miller EJ, Murthy VL, Birnie DH, Chen ES, Cooper LT, Tung RH, White ES, Borges-Neto S, Di Carli MF, Gropler RJ, Ruddy TD, Schindler TH and Blankstein R; EXPERT CONTENT REVIEWERS. Joint SNMMI-ASNC expert consensus document on the role of ^{18}F-FDG PET/CT in cardiac sarcoid detection and therapy monitoring. J Nucl Med 2017; 58: 1341-1353.

[4] Pandit-Taskar N, Postow MA, Hellmann MD, Harding JJ, Barker CA, O'Donoghue JA, Ziolkowska M, Ruan S, Lyashchenko SK, Tsai F, Farwell M, Mitchell TC, Korn R, Le W, Lewis JS, Weber WA, Behera D, Wilson I, Gordon M, Wu AM and Wolchok JD. First-in-humans imaging with ^{89}Zr-Df-IAB22M2C Anti-CD8 minibody in patients with solid malignancies: preliminary pharmacokinetics, biodistribution, and lesion targeting. J Nucl Med 2020; 61: 512-519.

[5] Shrestha U, Chae HD, Fang Q, Lee RJ, Packiasamy J, Huynh L, Blecha J, Huynh TL, VanBrocklin HF, Levi J and Seo Y. A feasibility study of [^{18}F]F-AraG positron emission

tomography (PET) for cardiac imaging-myocardial viability in ischemia-reperfusion injury model. Mol Imaging Biol 2024; 26: 869-878.

[6] Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, Becker JR, Slosky DA, Phillips EJ, Pilkinton MA, Craig-Owens L, Kola N, Plautz G, Reshef DS, Deutsch JS, Deering RP, Olenchock BA, Lichtman AH, Roden DM, Seidman CE, Koralnik IJ, Seidman JG, Hoffman RD, Taube JM, Diaz LA Jr, Anders RA, Sosman JA and Moslehi JJ. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 2016; 375: 1749-1755.

[7] Hirai T, Mayer AT, Nobashi TW, Lin PY, Xiao Z, Udagawa T, Seo K, Simonetta F, Baker J, Cheng AG, Negrin RS and Gambhir SS. Imaging alloreactive T cells provides early warning of organ transplant rejection. JCI Insight 2021; 6: e145360.

[8] Benichou G, Gonzalez B, Marino J, Ayasoufi K and Valujskikh A. Role of memory T cells in allograft rejection and tolerance. Front Immunol 2017; 8: 170.

[9] Hofmann U, Beyersdorf N, Weirather J, Podolskaya A, Bauersachs J, Ertl G, Kerkau T and Frantz S. Activation of CD4+ T lymphocytes improves wound healing and survival after experimental myocardial infarction in mice. Circulation 2012; 125: 1652-1663.

[10] Weirather J, Hofmann UD, Beyersdorf N, Ramos GC, Vogel B, Frey A, Ertl G, Kerkau T and Frantz S. Foxp3+ CD4+ T cells improve healing after myocardial infarction by modulating monocyte/macrophage differentiation. Circ Res 2014; 115: 55-67.

[11] Fernandez DM, Rahman AH, Fernandez NF, Chudnovskiy A, Amir ED, Amadori L, Khan NS, Wong CK, Shamailova R, Hill CA, Wang Z, Remark R, Li JR, Pina C, Faries C, Awad AJ, Moss N, Bjorkegren JLM, Kim-Schulze S, Gnjatic S, Ma'ayan A, Mocco J, Faries P, Merad M and Giannarelli C. Single-cell immune landscape of human atherosclerotic plaques. Nat Med 2019; 25: 1576-1588.

[12] Omidvari N, Levi J, Abdelhafez YG, Wang Y, Nardo L, Daly ME, Wang G and Cherry SR. Total-body dynamic imaging and kinetic modeling of [^{18}F]F-AraG in healthy individuals and a non-small cell lung cancer patient undergoing anti-PD-1 immunotherapy. J Nucl Med 2024; 65: 1481-1488.

[13] Farwell MD, Gamache RF, Babazada H, Hellmann MD, Harding JJ, Korn R, Mascioni A, Le W, Wilson I, Gordon MS, Wu AM, Ulaner GA, Wolchok JD, Postow MA and Pandit-Taskar N. CD8-targeted PET imaging of tumor-infiltrating T cells in patients with cancer: a phase I first-in-humans study of ^{89}Zr-Df-IAB22M2C, a radiolabeled anti-CD8 minibody. J Nucl Med 2022; 63: 720-726.

[14] Schwenck J, Sonanini D, Seyfried D, Ehrlichmann W, Kienzle G, Reischl G, Krezer P, Wilson I, Korn R, Gonzalez-Menendez I, Quintanilla-Martinez L, Seith F, Forschner A, Eigentler T, Zender L, Röcken M, Pichler BJ, Flatz L, Kneilling M and la Fougere C. *In vivo* imaging of CD8+ T cells in metastatic cancer patients: first clinical experience with simultaneous [^{89}Zr]Zr-Df-IAB22M2C PET/MRI. Theranostics 2023; 13: 2408-2423.

[15] Tavaré R, McCracken MN, Zettlitz KA, Salazar FB, Olafsen T, Witte ON and Wu AM. Immuno-PET of murine T cell reconstitution postadoptive stem cell transplantation using anti-CD4 and anti-CD8 cys-diabodies. J Nucl Med 2015; 56: 1258-1264.

[16] Freise AC, Zettlitz KA, Salazar FB, Lu X, Tavaré R and Wu AM. ImmunoPET imaging of murine CD4+ T cells using anti-CD4 cys-diabody: effects of protein dose on T cell function and imaging. Mol Imaging Biol 2017; 19: 599-609.

[17] Beckford Vera DR, Smith CC, Bixby LM, Glatt DM, Dunn SS, Saito R, Kim WY, Serody JS, Vincent BG and Parrott MC. Immuno-PET imaging of tumor-infiltrating lymphocytes using zirconium-89 radiolabeled anti-CD3 antibody in immune-competent mice bearing syngeneic tumors. PLoS One 2018; 13: e0193832.

[18] Di Gialleonardo V, Signore A, Glaudemans AW, Dierckx RA and De Vries EF. *N*-(4-^{18}F-fluorobenzoyl)interleukin-2 for PET of human-activated T lymphocytes. J Nucl Med 2012; 53: 679-686.

[19] van der Veen EL, Suurs FV, Cleeren F, Bormans G, Elsinga PH, Hospers GAP, Lub-de Hooge MN, de Vries EGE, de Vries EFJ and Antunes IF. Development and evaluation of interleukin-2-derived radiotracers for PET imaging of T cells in mice. J Nucl Med 2020; 61: 1355-1360.

[20] van der Veen EL, Antunes IF, Maarsingh P, Hessels-Scheper J, Zijlma R, Boersma HH, Jorritsma-Smit A, Hospers GAP, de Vries EGE, Lub-de Hooge MN and de Vries EFJ. Clinical-grade *N*-(4-[^{18}F]fluorobenzoyl)-interleukin-2 for PET imaging of activated T-cells in humans. EJNMMI Radiopharm Chem 2019; 4: 15.

[21] Nobashi TW, Mayer AT, Xiao Z, Chan CT, Chaney AM, James ML and Gambhir SS. Whole-body PET imaging of T-cell response to glioblastoma. Clin Cancer Res 2021; 27: 6445-6456.

[22] Glazer SE, Kummar S and Mittra E. Illuminating immunotherapy response via precision T cell-targeted PET imaging. Front Med (Lausanne) 2024; 11: 1233913.

[23] Niemeijer AN, Leung D, Huisman MC, Bahce I, Hoekstra OS, van Dongen GAMS, Boellaard R, Du S, Hayes W, Smith R, Windhorst AD, Hendrikse NH, Poot A, Vugts DJ, Thunnissen E, Morin P, Lipovsek D, Donnelly DJ, Bonacorsi SJ, Velasquez LM, de Gruijl TD, Smit EF and de Langen AJ. Whole body PD-1 and PD-L1 positron emission tomography in patients with non-small-cell lung cancer. Nat Commun 2018; 9: 4664.

[24] Niemeijer AN, Oprea-Lager DE, Huisman MC, Hoekstra OS, Boellaard R, de Wit-van der Veen BJ, Bahce I, Vugts DJ, van Dongen GAMS, Thunnissen E, Smit EF and de Langen AJ. Study of ^{89}Zr-pembrolizumab PET/CT in patients with advanced-stage non-small cell lung cancer. J Nucl Med 2022; 63: 362-367.

[25] Miedema IHC, Wijngaarden JE, Pouw JEE, Zwezerijnen GJC, Sebus HJ, Smit E, de Langen AJ, Bahce I, Thiele A, Vugts DJ, Boellaard R, Huisman MC and Menke-van der Houven van Oordt CW. ^{89}Zr-immuno-PET with immune checkpoint inhibitors: Measuring target engagement in healthy organs. Cancers (Basel) 2023; 15: 5546.

[26] Ehlerding EB, England CG, Majewski RL, Valdovinos HF, Jiang D, Liu G, McNeel DG, Nickles RJ and Cai W. ImmunoPET imaging of CTLA-4 expression in mouse models of non-small cell lung cancer. Mol Pharm 2017; 14: 1782-1789.

[27] Ehlerding EB, Lee HJ, Jiang D, Ferreira CA, Zahm CD, Huang P, Engle JW, McNeel DG and Cai W. Antibody and fragment-based PET imaging of CTLA-4+ T-cells in humanized mouse models. Am J Cancer Res 2019; 9: 53-63.

[28] Levi J, Lam T, Goth SR, Yaghoubi S, Bates J, Ren G, Jivan S, Huynh TL, Blecha JE, Khattri R, Schmidt KF, Jennings D and VanBrocklin H. Imaging of activated T cells as an early predictor of immune response to anti-PD-1 therapy. Cancer Res 2019; 79: 3455-3465.

[29] Levi J, Goth S, Huynh L, Lam T, Huynh TL, Schulte B and Packiasamy JA. ^{18}F-AraG PET for CD8 profiling of tumors and assessment of immunomodulation by chemotherapy. J Nucl Med 2021; 62: 802-807.

[30] Levi J, Duan H, Yaghoubi S, Packiasamy J, Huynh L, Lam T, Shaikh F, Behera D, Song H, Blecha J, Jivan S, Seo Y and VanBrocklin HF. Biodistribution of a mitochondrial metabolic tracer, [^{18}F]F-AraG, in healthy volunteers. Mol Imaging 2022; 2022: 3667417.

[31] Larimer BM, Wehrenberg-Klee E, Dubois F, Mehta A, Kalomeris T, Flaherty K, Boland G and Mahmood U. Granzyme B PET imaging as a predictive biomarker of immunotherapy response. Cancer Res 2017; 77: 2318-2327.

[32] LaSalle T, Austin EE, Rigney G, Wehrenberg-Klee E, Nesti S, Larimer B and Mahmood U. Granzyme B PET imaging of immune-mediated tumor killing as a tool for understanding immunotherapy response. J Immunother Cancer 2020; 8: e000291.

[33] Napier TS, Hunter CL, Song PN, Larimer BM and Sorace AG. Preclinical PET imaging of granzyme B shows promotion of immunological response following combination paclitaxel and immune checkpoint inhibition in triple negative breast cancer. Pharmaceutics 2022; 14: 440.

[34] Shen X, Zhou H, Zhou X, Liu Z, Meng X, Zhang L, Song Y, Guo R, Wang F, Li K, Li W, Yang Z, Liu Z and Li N. ^{68}Ga-grazytracer PET for noninvasive assessment of response to immunotherapy in solid tumors and lymphomas: a phase 1/2 clinical trial. Nat Commun 2024; 15: 8791.

[35] Tarkin JM, Joshi FR, Evans NR, Chowdhury MM, Figg NL, Shah AV, Starks LT, Martin-Garrido A, Manavaki R, Yu E, Kuc RE, Grassi L, Kreuzhuber R, Kostadima MA, Frontini M, Kirkpatrick PJ, Coughlin PA, Gopalan D, Fryer TD, Buscombe JR and Groves AM, Ouwehand WH, Bennett MR, Warburton EA, Davenport AP and Rudd JH. Detection of atherosclerotic inflammation by ^{68}Ga-DOTATATE PET compared to [^{18}F]FDG PET imaging. J Am Coll Cardiol 2017; 69: 1774-1791.

[36] Kircher M, Tran-Gia J, Kemmer L, Zhang X, Schirbel A, Werner RA, Buck AK, Wester HJ, Hacker M, Lapa C and Li X. Imaging inflammation in atherosclerosis with CXCR4-directed ^{68}Ga-Pentixafor PET/CT: Correlation with ^{18}F-FDG PET/CT. J Nucl Med 2020; 61: 751-756.

[37] Thackeray JT, Derlin T, Haghikia A, Napp LC, Wang Y, Ross TL, Schäfer A, Tillmanns J, Wester HJ, Wollert KC, Bauersachs J and Bengel FM. Molecular imaging of the chemokine receptor CXCR4 after acute myocardial infarction. JACC Cardiovasc Imaging 2015; 8: 1417-1426.

[38] Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P and Friedrich MG. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol 2018; 72: 3158-3176.