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*Review Article*

# Positron emission tomography probes for stem cell monitoring: a review

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**Abstract:** Stem cells possess unique self-renewal and differentiation capacities, that are central to cell replacement and tissue regeneration. The therapeutic potential of stem cell applications has garnered increasing attention in recent years for a spectrum of human diseases, from ischemic disorders to oncological challenges. Despite their potential, a comprehensive understanding of the biological behavior, efficacy, and safety of these cells remains elusive, hindering their clinical adoption. This review focuses on the use of positron emission tomography (PET) imaging as a cutting-edge tool for bridging this knowledge gap. PET imaging, a noninvasive diagnostic method, has been highlighted for its ability to monitor cellular dynamics after stem cell transplantation. A variety of molecular probes within the PET framework enable the longitudinal and quantitative evaluation of post-transplant cellular behavior. This discourse systematically delineates various PET probes specifically designed for the *in vivo* tracking of the stem cell life cycle. These probes offer a pathway to a deeper understanding and more precise evaluation of stem cell behavior post-transplantation. Implementing PET imaging probes can revolutionize the clinical understanding of stem cell behavior, advancing and widening clinical therapeutic applications.

**Keywords:** Stem cells, positron emission tomography imaging, molecular probes, in vivo tracking

## Introduction

Stem cells consist of a class of specialized cells with self-renewal and differentiation abilities that play a pivotal role in cell replacement and tissue regeneration [1-4], providing novel ideas and methods for effectively treating a variety of serious diseases. Pluripotent stem cells (PSCs) and multipotent stem cells can be categorized according to their differentiation potential. PSCs can differentiate into almost all cell types; for example, embryonic stem cells (ESCs) from the inner cell mass can differentiate to form any of the three embryonic layers but cannot form accessory supporting tissues such as the placenta and umbilical cord [5]. Multipotent stem cells can differentiate into closely related cell lineages, such as hematopoietic stem cells (HSCs), which can differentiate into cells of the blood and immune systems, such as red blood cells, white blood cells, and platelets [6]. PSCs include induced PSCs (iPSCs) [7, 8] and ESCs [9, 10], which can proliferate indefinitely and differentiate into all the body's cell types. Multipotent stem cells, such as mesenchymal stem cells (MSCs) [1, 11], HSCs [12], skeletal myoblasts [13], and endothelial progenitor cells [14, 15], can generate numerous cell types, but to a lesser extent than PSCs. Numerous studies have indicated that stem cell therapy is an option for treating ischemic diseases, neurodegenerative disorders, diabetes, and cancer. However, the efficacy of stem cell therapy and the *in vivo* contribution of stem cells remain elusive. Therefore, for preclinical cell therapy and subsequent clinical applications [16], assessing the efficacy, adaptability, and safety of stem cell therapy is of great significance. From this perspective, using positron emission tomography (PET) to analyze real-time images is essential.

A burgeoning multidisciplinary field, molecular imaging in nuclear medicine combines molecu-

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lar biology with modern medical imaging. This tool is significant for its ability to reflect intricate biological processes occurring within stem cells. Non-invasive methods provide researchers with the unique opportunity to observe and understand the inner workings of these cells without causing any harm or disturbance. This approach allows for the study of stem cells in their natural environment, producing more reliable and accurate results.

Moreover, PET, known as "biochemical imaging in vivo", provides noninvasive, quantitative, and dynamic observations of physiological, biochemical, and molecular processes from outside the body, offering insights into the activities of labeled subjects in vivo [17]. For these reasons, PET imaging allows noninvasive and longitudinal evaluation of the entire process of stem cell therapy for diseases [18, 19]. Researchers preparing for stem cell tracing usually begin by selecting tracer probes and labeling techniques suitable for specific stem cell types and study objectives. When initiating stem cell imaging tracing, researchers must consider probes, labeling methodologies, reporter genes, and stem cell types extensively [20].

For example, PET can be used to observe the uptake ratio of Alfatide II tracer in infarcted myocardium compared with normal myocardium, allowing assessment of the therapy response of bone marrow mesenchymal stem cells (BMSCs) [21]. This method can also monitor the homing of hematopoietic stem and progenitor cells (HSPCs) into the bone marrow after transplantation [22]. However, it is important to note that radiolabeling exerted significant toxicity on HSPCs 15 hours after labeling, indicating that the biosecurity of these radiolabeling techniques needs improvement. Additionally, PET can determine the effectiveness of various delivery methods for stem cell administration for treating chronic heart failure [23]. PET imaging has also been reported to achieve non-invasive visualization of stem cell distribution in multiple animal models [24].

The efficacy and safety of cell therapies are crucial for their success, as understanding the behavior of these cells within the body is essential. PET imaging provides valuable insight, allowing researchers to track the fate of these cells and determine whether they reach their intended targets. Furthermore, safety is of the utmost importance when developing cell-based treatments. PET imaging enables researchers to monitor side effects or adverse events associated with these therapies.

In conclusion, PET is a powerful noninvasive imaging method that can obtain cell functional information [24, 25]. It offers high sensitivity and can quantify the obtained data [26]. PET imaging evaluates the dynamics of stem cells *in vivo* and assesses the effectiveness and safety of cell therapies, assisting in revealing the underlying mechanisms of stem cell therapy and examining the body's response to these treatments. For example, chimeric antigen receptor T (CAR-T) cell immunotherapy is widely used in clinical practice [27, 28]. Currently, tumor biopsies [29, 30] and blood examinations are the primary means of evaluating their efficacy. However, these methods are invasive and not easily obtained. Researchers have developed a reporter gene imaging system using PET molecular imaging to monitor the *in vivo* dynamics of CAR-T cells [31-33]. This system enables precise identification of the position and number of CAR-T cells in living organisms [33-36].

In this review, we summarize various PET imaging methods associated with stem cells and introduce their advantages and limitations by comparing them. Furthermore, we discuss the current applications and limitations of PET in different diseases.

## PET imaging

PET imaging of stem cells (**Figure 1**) involves both direct and indirect labeling (i.e., reporter gene labeling) [37]. Direct labeling of stem cells has gained popularity in stem cell tracking studies over the past few decades. Using this technique, researchers can accurately trace the migration and differentiation of these cells in vivo [38]. By incorporating various labeling agents, such as superparamagnetic iron oxide nanoparticles or fluorescent dyes, scientists can visualize and monitor the behavior of stem cells noninvasively [39]. This has opened new possibilities for regenerative medicine and cell-based therapies. This method is frequently employed in stem cell imaging because of its convenience and low toxicity. However, it is important to acknowledge the drawbacks of

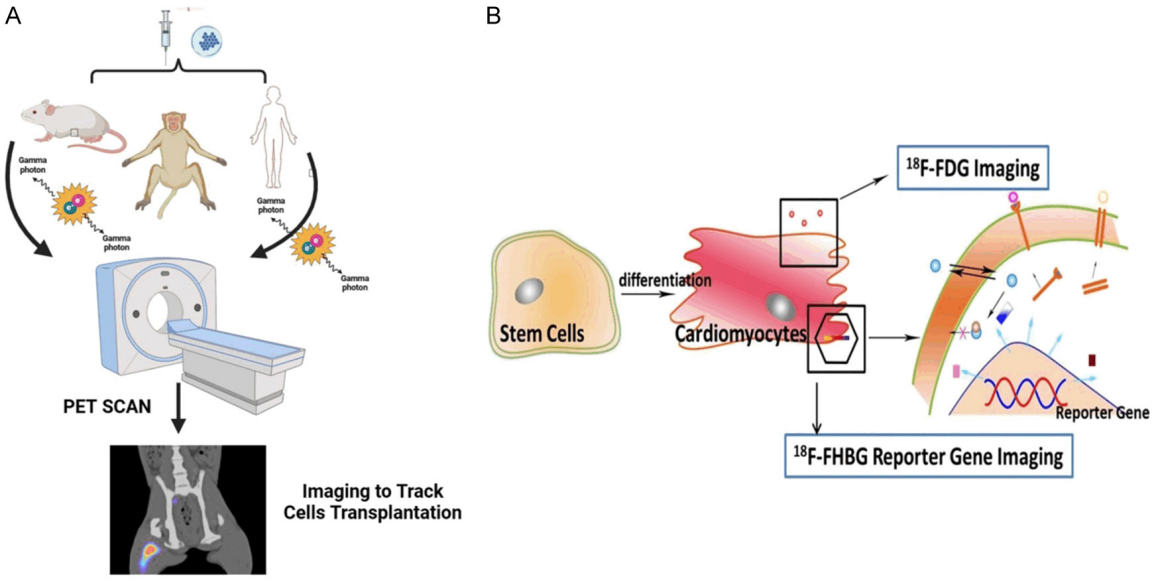


**Figure 1.** Schematic diagram of PET imaging for stem cell tracing. A. *In vivo*. B. Indirect labeling in cells. PET, positron emission tomography.

this method. Unstable labeling efficiency and signal dilution during cell division are significant disadvantages [40].

Before stem cell transplantation, it is essential to transfect the cells with plasmids, retroviruses, adenoviruses, or lentiviruses containing reporter genes. These genes play a crucial role in inducing cells to express specific enzymes, receptors, and fluorescent proteins [41]. The ability of the reporter gene to replicate within the cell genome ensures that the signal of this labeling approach is maintained even during cell division. This makes it a reliable and stable method for tracking and studying cellular processes over an extended period. Additionally, the signal intensity is directly correlated with the number of cells, which can be measured accurately [42].

In this section, we discuss strategies for direct labeling and reporter genes used in stem cell imaging. The efficiency of labeling is influenced by various factors, such as the cell type, labeling method, labeling time, labeling modification, probe, and reporter gene type.

## Direct labeling of stem cell imaging

### *$^{18}$F-FDG PET*

Fluorine-18-labeled agents, such as $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG), are extensively employed as radiotracers for stem cell labeling and *in vivo* tracking of dynamic biological distributions. These agents are representative of cellular absorption mediated by membrane transporters. Upon injection into the body, $^{18}$F-FDG is transported into cells through glucose transporters (Gluts) located on the cell membrane. In preclinical and clinical investigations, $^{18}$F-FDG has been used to label various types of stem cells and track their dynamics and biodistribution *in vivo*.

For example, the biodistribution of transplanted bone marrow-derived cells (BMCs) [37] in patients following myocardial infarction was tracked by labeling the BMCs with $^{18}$F-FDG and utilizing 3D PET imaging. Additionally, $^{18}$F-FDG has been used to investigate dynamic metabolic changes in a rat model of temporal lobe epilepsy after transplantation of human neural stem cells and human GABA progenitor cells [43]. Researchers have also used $^{18}$F-FDG to monitor BMCs in patients, contributing to a better understanding of their therapeutic use in myocardial infarction cases [44]. Based on these studies, $^{18}$F-FDG-PET/CT has become the preferred imaging method for evaluating the treatment response in multiple myeloma. According to these studies, $^{18}$F-FDG PET/CT may have prognostic and predictive significance in determining outcomes after autologous stem cell transplantation. However, longi-

tudinal imaging is severely limited by the short half-life of these agents ($^{18}$F, $t_{1/2}$ = 110 min).

*$^{111}$In-oxine labelled stem cells for single photon emission computed tomography*

$^{111}$In-oxine has been described by various papers because of its comparatively long half-life ($^{111}$In, $t_{1/2}$ = 67 h), making it suitable for exploring the long-term fate of MSCs in vivo [45]. $^{111}$In-oxine is widely accepted in the clinical settings [46]. Where the detection of infections and inflammation is crucial. Healthcare professionals rely on accurate and reliable methods to diagnose and treat these conditions promptly. Compared to $^{18}$F-FDG, $^{111}$In-oxine has a longer half-life, and its lipophilic property allows it to penetrate cell membranes easily, enabling prolonged imaging [47]. Additionally, $^{111}$In-oxine can be used to track extracellular vesicles derived from MSCs [48].

*$^{99m}$Tc-HMPAO*

$^{99m}$Tc-HMPAO, a technetium-labeled hexamethylpropyleneamine oxime, is widely applied in nuclear medicine for visualizing and analyzing cerebral blood flow and distribution in patients. This radiopharmaceutical has been extensively studied for its ability to identify localized inflammation [49]. It has also been investigated for its potential use in short-term stem cell imaging, primarily due to its short half-life of 6 hours [50], which is intermediate between $^{18}$F-FDG and $^{111}$In-oxine.

Compared to $^{111}$In-oxine, $^{99m}$Tc-HMPAO can be injected at higher dosages to enhance imaging quality due to its lower toxicity, allowing for a more precise and accurate assessment of the target area [51]. This capability makes $^{99}$mTc-HMPAO a valuable choice in imaging scenarios where higher resolution and clarity are desired, despite its poor retention and efficiency in radiolabeling.

### Reporter gene-based stem cell imaging

Unlike the three types of probes mentioned previously, reporter gene-based stem cell imaging is a cutting-edge technique that allows researchers to track and monitor the behavior of stem cells in real-time. By introducing a reporter gene into stem cells, scientists can use various imaging modalities, such as fluorescence or bioluminescence, to visualize and quantify their location, migration, and differentiation (**Figure 2**).

One representative reporter gene in the enzyme-substrate system is herpes simplex virus type I thymidine kinase (HSV1-39tk) or its mutant gene (HSV1-sr39tk). These can be combined with radionuclide-labeled probes for purine and pyrimidine nucleoside analogs (e.g., FIAU, FBAU, FHBG, and FPCV) [52]. Cells expressing HSV1-39tk can form radioactive concentrations, and the radioactivity of these cells reflects the expression of HSV1-39tk [53]. Additionally, HSV1-39tk can function as a suicide gene to provide an additional safety mechanism for abnormal cell behavior [54].

In the receptor-ligand system, representative reporter genes include somatostatin receptor 2 and dopamine 2 receptor. The somatostatin receptor 2 protein can reflect gene expression levels by binding and internalizing radiolabeled probes, such as $^{99m}$Tc-P829, $^{99m}$Tc-P2045, and $^{99m}$Tc-octreotide [55]. The dopamine 2 receptor is one of the few radionuclide reporter genes that can track cells in the brain, as $^{18}$F-FESP probes are highly liposoluble and can pass through the blood-brain barrier to target dopamine 2 receptors with high affinity [56].

The sodium-iodine symporter (NIS) reporter gene plays a crucial role in transporter-substrate systems. This gene serves as a representative reporter gene, providing valuable insight into the mechanisms and dynamics of these systems. The low expression of NIS in the body indicates a low background signal, promoting its application as an ideal reporter gene. NIS is not only a reporter gene but also a therapeutic gene for the radionuclide therapy of the thyroid [57].

Collectively, the current PET technique is relatively mature and widely applied in evaluating the efficacy of stem cell treatment. It contributes to understanding the effects of different stem cell injection methods, enabling researchers to observe the influence of stem cell therapy non-invasively. However, the potential toxicity of probes restricts the wide application of PET.

### Application of PET on monitoring stem cells

Transplanted stem cells have a remarkable ability to replace damaged or lost cells and

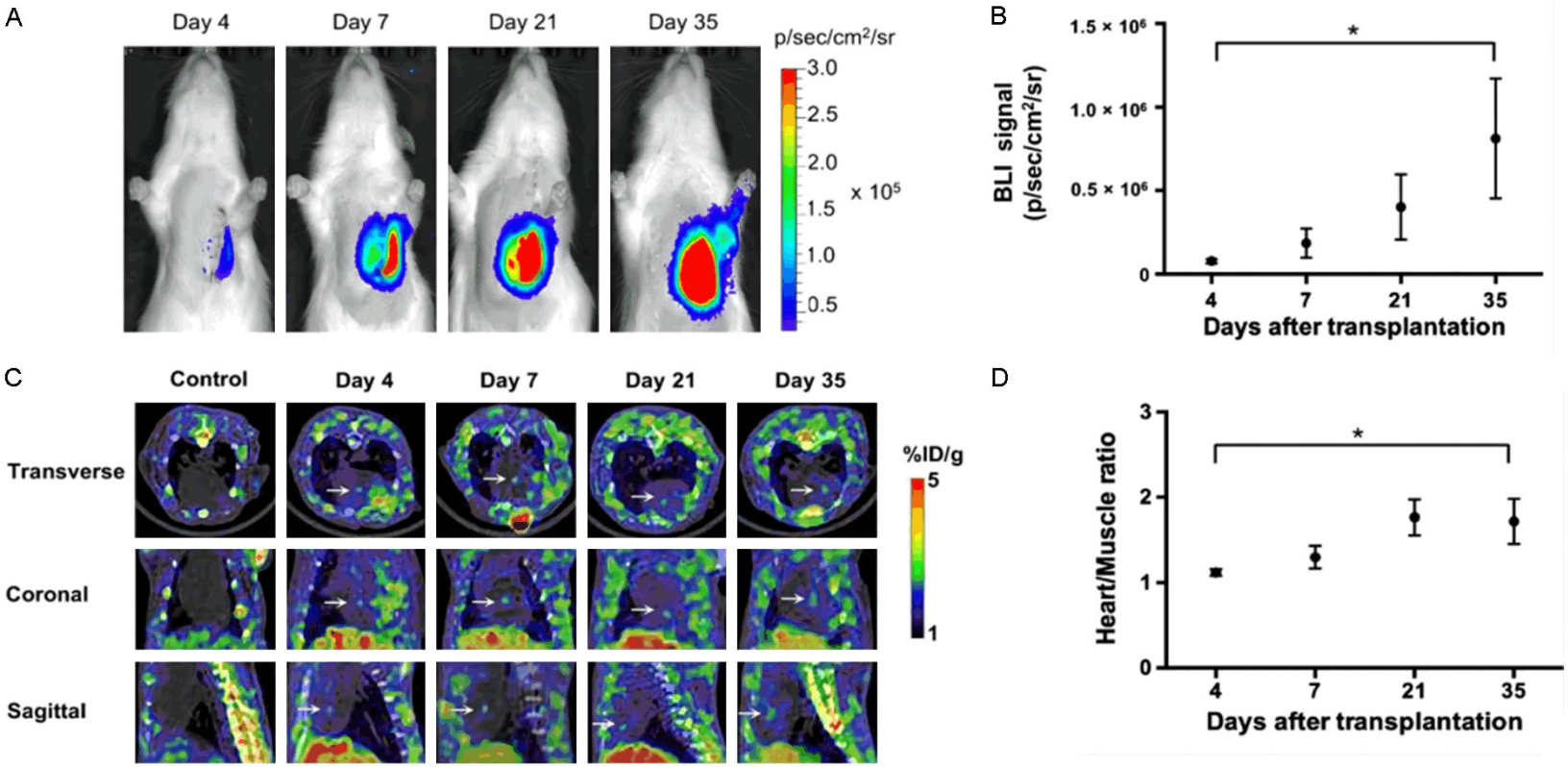


**Figure 2.** In vivo BLI and $^{18}$F-FHBG PET-CT imaging of TF-hUiCMs in infarcted rat hearts. A. Bioluminescence signals were captured at day 4, day 7, day 21, and day 35 after injection of TF-hUiCMs into the hearts of rats with myocardial infarction. B. Quantitative analysis of BLI signals in the TF-hUiCMs group. Signal activity is expressed as p/sec/cm$^2$/sr (n = 5). C. Representative $^{18}$F-FHBG PET-CT images (transverse, coronal, and sagittal) at Day 4, Day 7, Day 21, and Day 35. The white arrows indicate the transplanted cells. D. Heart-to-muscle ratio (H/M ratio) slightly increased over time (n = 5). *P<0.05. H/M ratio is decay-corrected max SUV of ROI of heart divided by decay-corrected max SUV of ROI of muscle [41].

interact with host cells, thereby enhancing their microenvironment and facilitating functional recovery. Stem cells are believed to boost tissue function in ischemia/reperfusion injury by replacing necrotic or nonfunctional host cells, inducing neovascularization, and recruiting resident stem cells [58]. Determining the *in vivo* effects and observing the distribution of stem cells is essential for subsequent therapy and application. Consequently, evaluating the therapeutic potential of stem cells requires advanced *in vivo* imaging techniques. Among these methods, PET is a potent molecular imaging technique that enables noninvasive and quantitative assessment of the efficacy of stem cell transplantation therapy. Various research groups have leveraged distinct PET probes to discern pathophysiological alterations resulting from stem cell therapy.

### Monitoring stem cell therapy in neurodegenerative disorders

The loss of neurons and glial cells in the central or peripheral nervous system is a key factor in the development of neurodegenerative disorders. Stem cells possess a unique ability to differentiate into various cell types, offering regeneration of damaged or lost neuronal and glial cells. This revolutionary concept provides hope for the treatment and management of neurodegenerative disorders.

Parkinson's disease is characterized by the progressive loss of dopaminergic neurons in the mesencephalic substantia nigra, leading to progressive behavioral abnormalities [59]. Using 11C-CFT PET/CT, researchers observed that BMSCs could induce a substantial increase in dopamine transporter expression, accompanied by modest and progressive improvement in motor activity [60]. Enhanced dopaminergic neurotransmission is crucial for determining the efficacy of L-DOPA treatment. Other dopamine transporter probes, such as $^{18}$F-FP-CIT, have also been used to assess the efficiency of stem cell treatments [61]. Additionally, PET tracers targeting dopamine precursor ligands and D2 receptors permit a more thorough evaluation of DA-specific activity [62].

When transplanted stem cells are used to treat Alzheimer's disease (AD), their primary mode of action involves interacting with host cells to provide therapeutic benefits. Stem cell therapy has shown potential in regenerating damaged brain tissues, improving cognitive function, and alleviating symptoms associated with AD. Neuroimaging with the amyloid beta radiotracer $^{18}$F-florbetapir demonstrated that human nasal turbinate stem cells significantly decreased amyloid beta levels and plaque formation in the brains of AD mice [63]. This is due to the powerful regulatory influence of human nasal turbinate stem cells on the immunological status of the host brain. They can decrease the number of microglial cells and the expression of the inflammatory cytokine IL-6, thereby increasing the survival rate of hippocampal and cortical neurons.

In general, PET probes such as $^{18}$F-FP-CIT have shown their ability in tracing stem cells in mouse disease models; however, this lacks human clinical evidence, and further investigation is needed for validation.

### Monitoring stem cell therapy in teratoma formation

Teratoma formation is a potential safety issue in stem cell therapy [64]. These tumors comprise various tissue types, including skin, hair, bone, and brain tissues [65-67]. Despite the immense therapeutic potential of stem cells, uncontrolled differentiation and proliferation during treatment can lead to the formation of postoperative teratomas. Therefore, researchers and clinicians must be vigilant about this safety issue and take measures to minimize the occurrence of teratomas during stem cell therapy. This includes strict cell screening, shorter cultivation times, and appropriate cell implantation methods. Only through scientific and standardized operations, as well as meticulous monitoring, can we ensure the safety of stem cell therapy and promote its development in clinical applications.

During the process of culturing and reprogramming ESCs, genetic abnormalities and the pluripotency of undifferentiated cells may lead to the development of teratomas [68]. Before transplantation, it is crucial to perform oncogenic mutation analysis and eliminate undifferentiated cells from the cultured stem cells. PET imaging technology enables *in vivo* monitoring of transplanted cells and the early diagnosis of teratomas. Reporter genes appear to be the most feasible candidates for long-term moni-

toring of transplanted stem cells despite the risk of genetic mutations [69]. However, recently developed site-specific gene integration techniques can mitigate this risk. Additionally, the PET reporter gene HSV-tk can function as a suicide gene in tumor ablation therapy [70, 71]. Targeting teratoma cell surface receptors could be another useful method for identifying tumor formation. Considering that each imaging modality has its advantages and limitations, the multi-modal approach may soon become the most reliable technique.

PET imaging, renowned for its sensitivity and the wide range of probes and imaging agents it offers, is an invaluable tool for studying various subjects, including small animals, large animals, and humans. Its versatility and accuracy make it indispensable in this field. For instance, a variety of imaging probes labeled with radioisotopes (e.g., $^{18}$F-ML-10 [71], $^{18}$F-FA3OP [72], $^{18}$F-Galacto-RGD [73], $^{18}$F-NaF [74]) have been used to trace biologic processes such as apoptosis, necrosis, angiogenesis, and scar formation. PET imaging using enzyme-based, receptor-based, and transporter-based reporter systems is a classic method for tracking stem cell fate. Combining PET with other imaging modalities, such as CT and MRI, provides anatomic structure references [75], essential for high-resolution stem cell imaging. Using a single modality, such as optical imaging, PET, MRI, or US, only partially elucidates specific aspects of stem cell biology, falling short of the requirements for both high resolution and sensitivity [76]. Integrating multiple imaging modalities confers a distinct advantage by leveraging the unique strengths of each, enabling fusion of functional and structural imaging to yield more precise physiological and pathologic information regarding stem cells *in vivo*.

In summary, PET not only monitors the efficacy of stem cell therapy post-transplantation but also observes potential side effects like teratoma formation. It is a non-invasive, convenient, and promising detection method, yet it has limitations that need addressing.

## Limitations

1. Immunogenicity concerns: Stem cell therapies hold significant therapeutic promise, but the heightened immunogenicity of stem cells presents challenges. Transplanting allogeneic stem cells can trigger immune responses, possibly leading to graft rejection and cell death. Despite efforts to minimize Major Histocompatibility Complex class I and II expression, certain stem cells like ESCs remain prone to immunological rejection. Monitoring cell viability and tracking the long-term fate of labeled stem cells are crucial yet challenging aspects of stem cell therapy.

2. Teratoma formation: The risk of teratoma or epidermoid cyst formation is a critical safety concern in stem cell therapy. Uncontrolled cell differentiation and proliferation can result in cyst formation, highlighting the necessity for rigorous cell screening, controlled culture durations, and precise implantation techniques. Genetic abnormalities acquired during embryonic stem cell culture and reprogramming further complicate this risk.

3. Limitations of reporter genes in PET imaging: PET imaging provides valuable insight into stem cell dynamics but is not without challenges, particularly regarding reporter genes. While these genes are useful for long-term cell monitoring, they can introduce genetic mutations. Although recent advancements in site-specific gene integration offer promise in reducing these risks, universal solutions are still in development.

4. Dependency on multiple imaging modalities: No single imaging modality offers a comprehensive view of stem cell biology, necessitating a multi-modal approach. Each imaging technique has unique strengths and limitations. Identifying the optimal combination of modalities to achieve comprehensive insights into stem cell behavior remains an active area of research.

## Challenges and conclusion

Stem cell therapy offers unprecedented opportunities for treating various diseases, especially neurodegenerative disorders. While PET imaging has significantly advanced the understanding and monitoring of stem cell therapy, addressing associated challenges is crucial. As stem cell research progresses, refining techniques, ensuring safety, and optimizing therapeutic efficacy remain paramount. Extending the half-life of PET probes without increasing toxicity is pivotal for their application in moni-

toring stem cell therapy. Current studies primarily focus on mouse models, thus more work is needed forclinical translation.

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## Disclosure of conflict of interest

None.

## Abbreviations

PET, positron emission tomography; PSCs, Pluripotent stem cells; iPSCs, induced pluripotent stem cells; ESCs, embryonic stem cells; MSCs, mesenchymal stem cells; HSCs, hematopoietic stem cells; CAR-T, chimeric antigen receptor T; ROI, region of interest; $^{18}$F-FDG, $^{18}$F-fluorodeoxyglucose; HSV1-39tk, herpes simplex virus type I thymidine kinase; NIS, Sodium-iodine symporter; OSEM, ordered-subset expectation maximization; AD, Alzheimer's disease.

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## References

[1] Fu X, Liu G, Halim A, Ju Y, Luo Q and Song AG. Mesenchymal stem cell migration and tissue repair. Cells 2019; 8: 784.

[2] Cheng H, Shang D and Zhou R. Germline stem cells in human. Signal Transduct Target Ther 2022; 7: 345.

[3] Saba JA, Liakath-Ali K, Green R and Watt FM. Translational control of stem cell function. Nat Rev Mol Cell Biol 2021; 22: 671-690.

[4] Zhang P, Dong J, Fan X, Yong J, Yang M, Liu Y, Zhang X, Lv L, Wen L, Qiao J, Tang F and Zhou Y. Characterization of mesenchymal stem cells in human fetal bone marrow by single-cell transcriptomic and functional analysis. Signal Transduct Target Ther 2023; 8: 126.

[5] De Miguel MP, Fuentes-Julián S and Alcaina Y. Pluripotent stem cells: origin, maintenance and induction. Stem Cell Rev Rep 2010; 6: 633-649.

[6] Sobhani A, Khanlarkhani N, Baazm M, Mohammadzadeh F, Najafi A, Mehdinejadiani S and Sargolzaei Aval F. Multipotent stem cell and current application. Acta Med Iran 2017; 55: 6-23.

[7] Aboul-Soud MAM, Alzahrani AJ and Mahmoud A. Induced Pluripotent Stem Cells (iPSCs)-roles in regenerative therapies, disease modelling and drug screening. Cells 2021; 10: 2319.

[8] Stoddard-Bennett T and Reijo Pera R. Treatment of Parkinson's disease through personalized medicine and induced pluripotent stem cells. Cells 2019; 8: 26.

[9] Hur YH, Feng S, Wilson KF, Cerione RA and Antonyak MA. Embryonic stem cell-derived extracellular vesicles maintain ESC stemness by activating FAK. Dev Cell 2021; 56: 277-291, e276.

[10] Golchin A, Chatziparasidou A, Ranjbarvan P, Niknam Z and Ardeshirylajimi A. Embryonic stem cells in clinical trials: current overview of developments and challenges. Adv Exp Med Biol 2021; 1312: 19-37.

[11] Al-Azab M, Safi M, Idiiatullina E, Al-Shaebi F and Zaky MY. Aging of mesenchymal stem cell: machinery, markers, and strategies of fighting. Cell Mol Biol Lett 2022; 27: 69.

[12] Demirci S, Leonard A and Tisdale JF. Hematopoietic stem cells from pluripotent stem cells: clinical potential, challenges, and future perspectives. Stem Cells Transl Med 2020; 9: 1549-1557.

[13] Rikhtegar R, Pezeshkian M, Dolati S, Safaie N, Afrasiabi Rad A, Mahdipour M, Nouri M, Jodati AR and Yousefi M. Stem cells as therapy for heart disease: iPSCs, ESCs, CSCs, and skeletal myoblasts. Biomed Pharmacother 2019; 109: 304-313.

[14] Mak A and Chan JKY. Endothelial function and endothelial progenitor cells in systemic lupus erythematosus. Nat Rev Rheumatol 2022; 18: 286-300.

[15] Bayraktutan U. Endothelial progenitor cells: potential novel therapeutics for ischaemic stroke. Pharmacol Res 2019; 144: 181-191.

[16] Brunet A, Goodell MA and Rando TA. Ageing and rejuvenation of tissue stem cells and their niches. Nat Rev Mol Cell Biol 2023; 24: 45-62.

[17] Cherk MH, Khor R, Barber TW, Yap KSK, Patil S, Walker P, Avery S, Roberts S, Kemp W, Pham A, Bailey M and Kalff V. Noninvasive assessment of acute graft-versus-host disease of the gastrointestinal tract after allogeneic hemopoietic stem cell transplantation using (18)F-FDG PET. J Nucl Med 2022; 63: 1899-1905.

[18] Nguyen PK, Riegler J and Wu JC. Stem cell imaging: from bench to bedside. Cell Stem Cell 2014; 14: 431-444.

[19] Tian M, He X, Jin C, He X, Wu S, Zhou R, Zhang X, Zhang K, Gu W, Wang J and Zhang H. Transpathology: molecular imaging-based pathology. Eur J Nucl Med Mol Imaging 2021; 48: 2338-2350.
[20] Parashurama N, Ahn BC, Ziv K, Ito K, Paulmurugan R, Willmann JK, Chung J, Ikeno F, Swanson JC, Merk DR, Lyons JK, Yerushalmi D, Teramoto T, Kosuge H, Dao CN, Ray P, Patel M, Chang YF, Mahmoudi M, Cohen JE, Goldstone AB, Habte F, Bhaumik S, Yaghoubi S, Robbins RC, Dash R, Yang PC, Brinton TJ, Yock PG, McConnell MV and Gambhir SS. Multimodality molecular imaging of cardiac cell transplantation: part II. In vivo imaging of bone marrow stromal cells in swine with PET/CT and MR imaging. Radiology 2016; 280: 826-836.
[21] Cai M, Ren L, Yin X, Guo Z, Li Y, He T, Tang Y, Long T, Liu Y, Liu G, Zhang X and Hu S. PET monitoring angiogenesis of infarcted myocardium after treatment with vascular endothelial growth factor and bone marrow mesenchymal stem cells. Amino Acids 2016; 48: 811-820.
[22] Faivre L, Chaussard M, Vercellino L, Vanneaux V, Hosten B, Teixera K, Parietti V, Merlet P, Sarda-Mantel L, Rizzo-Padoin N and Larghero J. (18)F-FDG labelling of hematopoietic stem cells: dynamic study of bone marrow homing by PET-CT imaging and impact on cell functionality. Curr Res Transl Med 2016; 64: 141-148.
[23] Elhami E, Dietz B, Xiang B, Deng J, Wang F, Chi C, Goertzen AL, Mzengeza S, Freed D, Arora RC and Tian G. Assessment of three techniques for delivering stem cells to the heart using PET and MR imaging. EJNMMI Res 2013; 3: 72.
[24] Nose N, Nogami S, Koshino K, Chen X, Werner RA, Kashima S, Rowe SP, Lapa C, Fukuchi K and Higuchi T. [18F]FDG-labelled stem cell PET imaging in different route of administrations and multiple animal species. Sci Rep 2021; 11: 10896.
[25] Campbell BA, Brown R, Lambertini A, Hofman MS, Bressel M, Seymour JF, Wirth A, MacManus M and Dickinson M. Are dynamic or fixed FDG-PET measures of disease of greater prognostic value in patients with relapsed/refractory diffuse large B-cell lymphoma undergoing autologous haematopoietic stem cell transplantation? Br J Haematol 2023; 201: 502-509.
[26] Rahmim A, Lodge MA, Karakatsanis NA, Panin VY, Zhou Y, McMillan A, Cho S, Zaidi H, Casey ME and Wahl RL. Dynamic whole-body PET imaging: principles, potentials and applications. Eur J Nucl Med Mol Imaging 2019; 46: 501-518.
[27] Zhang P, Yang X, Cao Y, Wang J, Zhou M, Chen L, Wei J, Mao Z, Wang D, Xiao Y, Zhu H, Zhang S, Zhang T, Zhang Y, Zhou J and Huang L. Autologous stem cell transplantation in tandem with anti-CD30 CAR T-cell infusion in relapsed/refractory CD30(+) lymphoma. Exp Hematol Oncol 2022; 11: 72.
[28] Mohammadi M, Akhoundi M, Malih S, Mohammadi A and Sheykhhasan M. Therapeutic roles of CAR T cells in infectious diseases: clinical lessons learnt from cancer. Rev Med Virol 2022; 32: e2325.
[29] Larson RC, Kann MC, Bailey SR, Haradhvala NJ, Llopis PM, Bouffard AA, Scarfó I, Leick MB, Grauwet K, Berger TR, Stewart K, Anekal PV, Jan M, Joung J, Schmidts A, Ouspenskaia T, Law T, Regev A, Getz G and Maus MV. CAR T cell killing requires the IFNγR pathway in solid but not liquid tumours. Nature 2022; 604: 563-570.
[30] Feucht J and Abou-El-Enein M. Senolytic CAR T cells in solid tumors and age-related pathologies. Mol Ther 2020; 28: 2108-2110.
[31] Shao F, Long Y, Ji H, Jiang D, Lei P and Lan X. Radionuclide-based molecular imaging allows CAR-T cellular visualization and therapeutic monitoring. Theranostics 2021; 11: 6800-6817.
[32] Murty S, Labanieh L, Murty T, Gowrishankar G, Haywood T, Alam IS, Beinat C, Robinson E, Aalipour A, Klysz DD, Cochran JR, Majzner RG, Mackall CL and Gambhir SS. PET reporter gene imaging and ganciclovir-mediated ablation of chimeric antigen receptor T cells in solid tumors. Cancer Res 2020; 80: 4731-4740.
[33] Sellmyer MA, Richman SA, Lohith K, Hou C, Weng CC, Mach RH, O'Connor RS, Milone MC and Farwell MD. Imaging CAR T cell trafficking with eDHFR as a PET reporter gene. Mol Ther 2020; 28: 42-51.
[34] Lee IK, Noguera-Ortega E, Xiao Z, Todd L, Scholler J, Song D, Liousia M, Lohith K, Xu K, Edwards KJ, Farwell MD, June CH, Albelda SM, Puré E and Sellmyer MA. Monitoring therapeutic response to anti-FAP CAR T cells using [18F]AlF-FAPI-74. Clin Cancer Res 2022; 28: 5330-5342.
[35] Adusumilli PS, Zauderer MG, Rivière I, Solomon SB, Rusch VW, O'Cearbhaill RE, Zhu A, Cheema W, Chintala NK, Halton E, Pineda J, Perez-Johnston R, Tan KS, Daly B, Araujo Filho JA, Ngai D, McGee E, Vincent A, Diamonte C, Sauter JL, Modi S, Sikder D, Senechal B, Wang X, Travis WD, Gönen M, Rudin CM, Brentjens RJ, Jones DR and Sadelain M. A phase I trial of regional mesothelin-targeted CAR T-cell therapy in patients with malignant pleural disease, in combination with the anti-PD-1 agent pembrolizumab. Cancer Discov 2021; 11: 2748-2763.
[36] Mulholland N, Chandra J, Sanderson R and Kuhnl A. Chimeric antigen receptor T-cell ther-

apy and imaging applications for large B-cell lymphoma. Radiology 2023; 307: e221362.
[37] Hofmann M, Wollert KC, Meyer GP, Menke A, Arseniev L, Hertenstein B, Ganser A, Knapp WH and Drexler H. Monitoring of bone marrow cell homing into the infarcted human myocardium. Circulation 2005; 111: 2198-2202.
[38] Kim MH, Lee YJ and Kang JH. Stem cell monitoring with a direct or indirect labeling method. Nucl Med Mol Imaging 2016; 50: 275-283.
[39] Mahmoudi M, Hosseinkhani H, Hosseinkhani M, Boutry S, Simchi A, Journeay WS, Subramani K and Laurent S. Magnetic resonance imaging tracking of stem cells in vivo using iron oxide nanoparticles as a tool for the advancement of clinical regenerative medicine. Chem Rev 2011; 111: 253-280.
[40] Gawne PJ, Man F, Blower PJ and T M de Rosales R. Direct cell radiolabeling for in vivo cell tracking with PET and SPECT imaging. Chem Rev 2022; 122: 10266-10318.
[41] Attia N, Mashal M, Puras G and Pedraz JL. Mesenchymal stem cells as a gene delivery tool: promise, problems, and prospects. Pharmaceutics 2021; 13: 843.
[42] Ha T, Kaiser C, Myong S, Wu B and Xiao J. Next generation single-molecule techniques: imaging, labeling, and manipulation in vitro and in cellulo. Mol Cell 2022; 82: 304-314.
[43] Du R, Zhu X, Wu S, Zhang X, He Y, Zhang K, He X, Wang X, Sun Y, Wang Q, Zhang H and Tian M. PET imaging of metabolic changes after neural stem cells and GABA progenitor cells transplantation in a rat model of temporal lobe epilepsy. Eur J Nucl Med Mol Imaging 2019; 46: 2392-2397.
[44] Jacene HA. FDG PET for assessment of autologous stem cell transplantation. Semin Nucl Med 2021; 51: 380-391.
[45] Elster JL, Rathbone CR, Liu Z, Liu X, Barrett HH, Rhoads RP and Allen RE. Skeletal muscle satellite cell migration to injured tissue measured with 111In-oxine and high-resolution SPECT imaging. J Muscle Res Cell Motil 2013; 34: 417-427.
[46] Ruf J, Oeser C and Amthauer H. Clinical role of anti-granulocyte MoAb versus radiolabeled white blood cells. Q J Nucl Med Mol Imaging 2010; 54: 599-616.
[47] Malviya G, Nayak T, Gerdes C, Dierckx RA, Signore A and de Vries EF. Isolation and (111)In-oxine labeling of murine NK cells for assessment of cell trafficking in orthotopic lung tumor model. Mol Pharm 2016; 13: 1329-1338.
[48] Lu CH, Chen YA, Ke CC, Chiu SJ, Chen CC, Hsieh YJ, Yang BH and Liu RS. Preclinical characterization and in vivo imaging of (111)In-labeled mesenchymal stem cell-derived extracellular vesicles. Mol Imaging Biol 2021; 23: 361-371.
[49] Kim EM, Oh PS, Boud F, Jeong HJ, Lim ST and Sohn MH. Rodent leukocyte isolation and radiolabeling for inflammation imaging study. Nucl Med Mol Imaging 2020; 54: 147-155.
[50] Detante O, Moisan A, Dimastromatteo J, Richard MJ, Riou L, Grillon E, Barbier E, Desruet MD, De Fraipont F, Segebarth C, Jaillard A, Hommel M, Ghezzi C and Remy C. Intravenous administration of 99mTc-HMPAO-labeled human mesenchymal stem cells after stroke: in vivo imaging and biodistribution. Cell Transplant 2009; 18: 1369-1379.
[51] Welling MM, Duijvestein M, Signore A and van der Weerd L. In vivo biodistribution of stem cells using molecular nuclear medicine imaging. J Cell Physiol 2011; 226: 1444-1452.
[52] Gambhir SS, Bauer E, Black ME, Liang Q, Kokoris MS, Barrio JR, Iyer M, Namavari M, Phelps ME and Herschman HR. A mutant herpes simplex virus type 1 thymidine kinase reporter gene shows improved sensitivity for imaging reporter gene expression with positron emission tomography. Proc Natl Acad Sci U S A 2000; 97: 2785-2790.
[53] Gao Y, Wu S, Pan J, Zhang K, Li X, Xu Y, Jin C, He X, Shi J, Ma L, Wu F, Yao Y, Wang P, He Q, Lan F, Zhang H and Tian M. CRISPR/Cas9-edited triple-fusion reporter gene imaging of dynamics and function of transplanted human urinary-induced pluripotent stem cell-derived cardiomyocytes. Eur J Nucl Med Mol Imaging 2021; 48: 708-720.
[54] Zhang L, Zhuang X, Kotitalo P, Keller T, Krzyczmonik A, Haaparanta-Solin M, Solin O, Forsback S, Grönroos TJ, Han C, López-Picón FR and Xia H. Intravenous transplantation of olfactory ensheathing cells reduces neuroinflammation after spinal cord injury via interleukin-1 receptor antagonist. Theranostics 2021; 11: 1147-1161.
[55] Ahmed N, Ammar A, Bashir K, Fatima S, Zia M, Saeed MA and Faheem M. Comparative evaluation of 99mTc-octreotide for diagnostic accuracy assessment and localization of 177Lu-DOTA-TATE in neuroendocrine tumors. Curr Med Imaging 2023; [Epub ahead of print].
[56] Vandeputte C, Evens N, Toelen J, Deroose CM, Bosier B, Ibrahimi A, Van der Perren A, Gijsbers R, Janssen P, Lambert DM, Verbruggen A, Debyser Z, Bormans G, Baekelandt V and Van Laere K. A PET brain reporter gene system based on type 2 cannabinoid receptors. J Nucl Med 2011; 52: 1102-1109.
[57] Nikitski AV, Condello V, Divakaran SS and Nikiforov YE. Inhibition of ALK-signaling overcomes STRN-ALK-induced downregulation of the sodium iodine symporter and restores radioiodine uptake in thyroid cells. Thyroid 2023; 33: 464-473.

[58] Cai M, Shen R, Song L, Lu M, Wang J, Zhao S, Tang Y, Meng X, Li Z and He ZX. Bone Marrow Mesenchymal Stem Cells (BM-MSCs) improve heart function in swine myocardial infarction model through paracrine effects. Sci Rep 2016; 6: 28250.

[59] Park S, Kim E, Koh SE, Maeng S, Lee WD, Lim J, Shim I and Lee YJ. Dopaminergic differentiation of neural progenitors derived from placental mesenchymal stem cells in the brains of Parkinson's disease model rats and alleviation of asymmetric rotational behavior. Brain Res 2012; 1466: 158-166.

[60] Hayashi T, Wakao S, Kitada M, Ose T, Watabe H, Kuroda Y, Mitsunaga K, Matsuse D, Shigemoto T, Ito A, Ikeda H, Fukuyama H, Onoe H, Tabata Y and Dezawa M. Autologous mesenchymal stem cell-derived dopaminergic neurons function in parkinsonian macaques. J Clin Invest 2013; 123: 272-284.

[61] Park BN, Kim JH, Lee K, Park SH and An YS. Improved dopamine transporter binding activity after bone marrow mesenchymal stem cell transplantation in a rat model of Parkinson's disease: small animal positron emission tomography study with F-18 FP-CIT. Eur Radiol 2015; 25: 1487-1496.

[62] Muramatsu S, Okuno T, Suzuki Y, Nakayama T, Kakiuchi T, Takino N, Iida A, Ono F, Terao K, Inoue N, Nakano I, Kondo Y and Tsukada H. Multitracer assessment of dopamine function after transplantation of embryonic stem cell-derived neural stem cells in a primate model of Parkinson's disease. Synapse 2009; 63: 541-548.

[63] Lim JY, In Park S, Park SA, Jeon JH, Jung HY, Yon JM, Jeun SS, Lim HK and Kim SW. Potential application of human neural crest-derived nasal turbinate stem cells for the treatment of neuropathology and impaired cognition in models of Alzheimer's disease. Stem Cell Res Ther 2021; 12: 402.

[64] Zakrzewski W, Dobrzyński M, Szymonowicz M and Rybak Z. Stem cells: past, present, and future. Stem Cell Res Ther 2019; 10: 68.

[65] Garcia-Aguilar P, Maiz N, Rodó C, Garcia-Manau P, Arévalo S, Molino JA, Guillen G and Carreras E. Fetal abdominal cysts: predicting adverse outcomes. Acta Obstet Gynecol Scand 2023; 102: 883-890.

[66] Boody BS and Savage JW. Evaluation and treatment of lumbar facet cysts. J Am Acad Orthop Surg 2016; 24: 829-842.

[67] Shimizu T, Yoshioka M, Kaneya Y, Kanda T, Aoki Y, Kondo R, Takata H, Ueda J, Kawano Y, Hirakata A, Matsushita A, Taniai N, Mamada Y and Yoshida H. Management of simple hepatic cyst. J Nippon Med Sch 2022; 89: 2-8.

[68] Neyrinck K, Breuls N, Holvoet B, Oosterlinck W, Wolfs E, Vanbilloen H, Gheysens O, Duelen R, Gsell W, Lambrichts I, Himmelreich U, Verfaillie CM, Sampaolesi M and Deroose CM. The human somatostatin receptor type 2 as an imaging and suicide reporter gene for pluripotent stem cell-derived therapy of myocardial infarction. Theranostics 2018; 8: 2799-2813.

[69] Wolfs E, Holvoet B, Ordovas L, Breuls N, Helsen N, Schönberger M, Raitano S, Struys T, Vanbilloen B, Casteels C, Sampaolesi M, Van Laere K, Lambrichts I, Verfaillie CM and Deroose CM. Molecular imaging of human embryonic stem cells stably expressing human PET reporter genes after zinc finger nuclease-mediated genome editing. J Nucl Med 2017; 58: 1659-1665.

[70] Zhou H, Liu H, Zhang Y, Xin Y, Huang C, Li M, Zhao X, Ding P and Liu Z. "PFH/AGM-CBA/HSV-TK/LIPOSOME-Affibody": novel targeted nano ultrasound contrast agents for ultrasound imaging and inhibited the growth of ErbB2-overexpressing gastric cancer cells. Drug Des Devel Ther 2022; 16: 1515-1530.

[71] Sawdon AJ, Zhang J, Peng S, Alyami EM and Peng CA. Polymeric nanovectors incorporated with ganciclovir and HSV-tk encoding plasmid for gene-directed enzyme prodrug therapy. Molecules 2021; 26: 1759.

[72] Zhang D, Jiang C, Feng Y, Ni Y and Zhang J. Molecular imaging of myocardial necrosis: an updated mini-review. J Drug Target 2020; 28: 565-573.

[73] Makowski MR, Rischpler C, Ebersberger U, Keithahn A, Kasel M, Hoffmann E, Rassaf T, Kessler H, Wester HJ, Nekolla SG, Schwaiger M and Beer AJ. Multiparametric PET and MRI of myocardial damage after myocardial infarction: correlation of integrin αvβ3 expression and myocardial blood flow. Eur J Nucl Med Mol Imaging 2021; 48: 1070-1080.

[74] Marchesseau S, Seneviratna A, Sjöholm AT, Qin DL, Ho JXM, Hausenloy DJ, Townsend DW, Richards AM, Totman JJ and Chan MYY. Hybrid PET/CT and PET/MRI imaging of vulnerable coronary plaque and myocardial scar tissue in acute myocardial infarction. J Nucl Cardiol 2018; 25: 2001-2011.

[75] Jurgielewicz P, Harmsen S, Wei E, Bachmann MH, Ting R and Aras O. New imaging probes to track cell fate: reporter genes in stem cell research. Cell Mol Life Sci 2017; 74: 4455-4469.

[76] He XY, Zhou YR, Mu T, Liao YF, Jiang L, Qin Y and Cai JH. Magnetic resonance imaging focused on the ferritin heavy chain 1 reporter gene detects neuronal differentiation in stem cells. Neural Regen Res 2023; 18: 1563-1569.