

## Contributed Mini Review

# In vivo exosome imaging: applications of diverse visualization techniques

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Exosomes—nanoscale extracellular vesicles secreted by various cell types—play a crucial role in intercellular communication by delivering biologically active molecules, such as proteins, nucleic acids, and lipids. Due to their intrinsic biocompatibility, targeting capabilities, and stability, exosomes have emerged as promising vehicles for diagnostics and therapeutics in a wide range of diseases, including cancer, and neurodegenerative, cardiovascular, and autoimmune disorders. The ability to monitor exosome biodistribution and dynamics *in vivo* is pivotal to promoting their clinical translation. This review provides a comprehensive overview of the current visualization techniques employed for *in vivo* exosome imaging: optical imaging, magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and emerging modalities, such as photoacoustic imaging, ultrasound, and Raman-based approaches. The advantages, limitations, and representative applications of each imaging modality are critically discussed, with emphasis on labeling strategies that enhance tracking sensitivity and specificity. Optical imaging offers high sensitivity, but is limited by shallow tissue penetration, whereas MRI provides excellent spatial resolution, but suffers from low molecular sensitivity. Radionuclide-based imaging, such as PET and SPECT, enables highly sensitive, quantitative tracking, but presents challenges regarding radiotracer stability and safety. Emerging multimodal platforms and labeling innovations are highlighted for their potential to overcome current limitations. Future research di-

rections include the development of non-invasive, highly sensitive, and clinically translatable imaging systems, as well as standardized protocols to ensure reproducibility. Advances in exosome imaging technologies will be instrumental to unlock the full diagnostic and therapeutic potential of exosome-based platforms in precision medicine. [BMB Reports 2025; 58(8): 340-349]

## INTRODUCTION

Exosomes are small extracellular vesicles of (30-200) nm size that are present in various organ tissues and body fluids (1). They mediate intercellular communication by carrying bioactive molecules, such as DNA, RNAs, proteins, and lipids (2). Exosomes contribute to various diseases, and due to their biocompatibility and targeting ability, hold promise as diagnostic tools and therapeutic carriers (3-9). Studies are using non-invasive, stable monitoring techniques to examine *in vivo* exosome roles to extensively elucidate the physiological mechanisms and therapeutic potential of exosomes (10). Ongoing clinical trials and FDA-approved exosome-based therapies underline the urgent need for robust imaging technologies to enhance understanding of exosome biology. For example, clinical investigations of exosome for cancer immunotherapy and regenerative medicine demonstrate the translational potential of exosome research. *In vivo*, exosome imaging can address pivotal clinical challenges, such as improving cancer treatment precision, enabling early neurodegenerative disease detection, and refining therapeutic delivery systems. This review introduces various *in vivo* exosome imaging strategies (Fig. 1), discusses their advantages and limitations (Table 1), and highlights representative research cases that demonstrate potential clinical applications.

## OPTICAL IMAGING

An overview of major *in vivo* exosome labeling strategies and corresponding imaging modalities is schematically illustrated in (Fig. 1). Due to its high sensitivity and real-time visualization

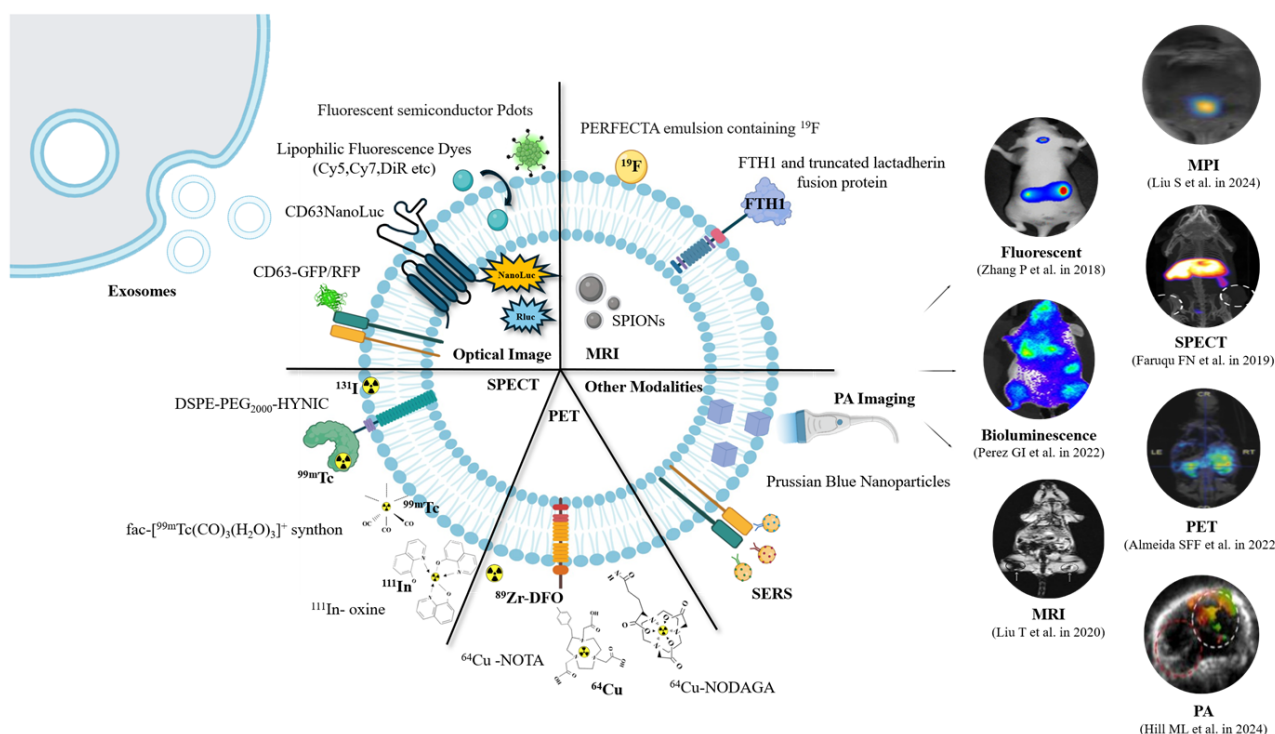
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**Fig. 1.** Schematic overview of *in vivo* exosome imaging modalities and labeling strategies. Major imaging modalities and representative labeling strategies for tracking exosomes *in vivo* are summarized. The central schematic illustrates various methods to label exosomes, including lipophilic fluorescent dyes, genetically encoded reporters, radioisotopes, and other nanoparticles. The right panel displays representative *in vivo* exosome images acquired from different techniques.

capabilities, optical imaging, including fluorescence and bioluminescence imaging, is widely used in exosome research (11). Fluorescence imaging relies on external light to excite fluorescent probes, while bioluminescence imaging detects light produced by enzyme-catalyzed reactions, without external illumination. Bioluminescence imaging offers lower background and higher sensitivity, whereas fluorescence imaging provides more probe options. Recent developments in multifunctional optical imaging platforms integrate fluorescence and bioluminescent probes for more precise exosome tracking.

### Fluorescence imaging

Fluorescence imaging, which uses fluorophores that are excited by an external light source, is advantageous for non-invasive *in vivo* monitoring, because fluorescence labeling is relatively simple, and widely applicable. While various fluorescent probes have been developed for *in vivo* imaging (12), they have limited tissue penetration depth and low spatial resolution, which poses exosome tracking challenges in deep tissues. Also, some lipophilic fluorescent dyes may compromise imaging reliability by inducing exosome aggregation (13).

Fluorescence imaging is widely used to visualize the bio-distribution and dynamics of fluorescent dye-labeled exosomes

or proteins in real time. This approach enables the tracking of tissue-specific exosome distribution and dynamic changes, providing critical insight into physiological and pathological processes, along with drug delivery and disease diagnosis (14). In general, fluorescent dyes are classified into the visible light and near-infrared (NIR) regions ranging ([400-700] and [700-900] nm, respectively. Although visible light dyes offer high quantum efficiency and strong fluorescence signals, they are limited in penetration depth. Thus, in thick tissues, signal attenuation and scattering can hinder accurate imaging (15). Furthermore, high background tissue autofluorescence can reduce the signal-to-noise ratio, making accurate quantitative analysis significantly challenging (16). In contrast, NIR dyes are more suitable for *in vivo* exosome tracking, because they minimize background signal via deeper tissue penetration and lower autofluorescence (17). These advantages have resulted in NIR dyes becoming a key exosome imaging tool; while in preclinical studies, they play a crucial role in quantitative exosome biodistribution and target organ accumulation analyses (18). In addition to dye-based labeling, exosomes can be tracked by genetically encoding fluorescent proteins fused to exosome-enriched membrane proteins. For example, CD63 fused with GFP enables the real-time monitoring of exosome

dynamics in live animals. A representative study demonstrated this approach using a Sox2 promoter-driven CD63–GFP transgenic rat model, which allowed for the *in vivo* tracking of neural stem cell-derived Exosomes (19). Notably, labeling exosome membrane proteins with fluorescent proteins may induce structural and functional alterations, potentially affecting their biological properties (15). The DiR (1,1'-dioctadecyl-3,3,3',3'-tetramethylindotricarbocyanine iodide), a NIR fluore-

scent probe with an emission range of (750-900) nm, is widely used to track *in vivo* exosome distribution. A recent study used DiR-labeled mesenchymal stem cell (MSC)-derived exosomes to evaluate their tumor-targeting ability in an osteosarcoma model *in vivo* (20). The cyanine-based fluorescent dyes, Cy5 and Cy7 of (670 and [767-780]) nm, which emit fluorescence in the red and NIR ranges, respectively, are widely used to track exosome *in vivo* biodistribution (21). However, because

**Table 1.** Comparative analysis of imaging technologies for *in vivo* exosome tracking

| Modality                        | Labeling strategy                                                     | Representative probes                            | Purpose                                                         | Animal model                                | Admin   | Advantages                                                                     | Limitations                                                        | Ref.             |
|---------------------------------|-----------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------|---------|--------------------------------------------------------------------------------|--------------------------------------------------------------------|------------------|
| Fluorescence                    | Lipophilic dyes<br>Genetic reporters<br>Pdot                          | DBCO-Cy5/Cy7,<br>CD63-GFP                        | Tumor targeting,<br>Stem cell tracking                          | Osteosarcoma mice,<br>Transgenic rats       | IV, Edg | High sensitivity<br>Real-time imaging<br>NIR: deep penetration, low background | Shallow penetration<br>Low resolution<br>Potential for aggregation | (17, 19, 20, 23) |
| Bioluminescence (BLI)           | Fusing luciferase enzymes to exosome proteins                         | RLuc, CD63-NanoLuc                               | Biodistribution, Cardiac exosome tracking, Long-term monitoring | Tumor-bearing mice, Transgenic mice         | Edg     | Very high sensitivity<br>Low background signal<br>Quantitative                 | Signal loss with depth<br>Surface-weighted signals                 | (27, 29, 31)     |
| MRI                             | Contrast agents ( <sup>19</sup> F SPIONs)<br>Genetic reporters (FTH1) | SPIONs, FTH1                                     | Biodistribution, MSC tracking, Mapping protein interactions     | C57BL/6 mice                                | IV      | High spatial resolution<br>Deep penetration<br>No radiation                    | Low sensitivity<br>High cost<br>Long scan times                    | (38-40)          |
| Magnetic Particle Imaging (MPI) | Loading exosomes with SPIONs via parent cells                         | SPIONs                                           | Tumor targeting                                                 | Brain metastasis mice, Prostate cancer mice | IV      | Very high sensitivity<br>No background signal<br>Long term tracking            | Emerging technology<br>Preclinical stage only                      | (46, 47)         |
| SPECT                           | Labeling with gamma emitting radionuclides                            | <sup>111</sup> In-oxine, <sup>99m</sup> Tc-HMPAO | Dynamic monitoring, Tumor imaging                               | Tumor bearing nude mice, BALB/c mice        | IV      | High sensitivity<br>Uses long lived tracers                                    | Low spatial resolution<br>Lower quantitative accuracy              | (53, 55, 57)     |
| PET                             | Labeling with positron emitting radionuclides                         | <sup>89</sup> Zr-DFO<br><sup>64</sup> Cu-NOTA    | Quantitative PK, Metastasis imaging, EPR effect study           | Nude mice, Breast cancer mice               | IV      | Extremely high sensitivity<br>Excellent for quantification<br>Deep penetration | Short half-life of tracers<br>Requires cyclotron                   | (66-68)          |
| Photoacoustic Imaging (PAI)     | Hybridizing exosomes with PAI contrast agents                         | Exosome PBNP hybrids                             | Targeted glioblastoma detection                                 | Glioblastoma mice                           | IV      | Hybrid: deep penetration + high specificity<br>No radiation, cost effective    | Emerging technology<br>Needs standardization                       | (72)             |
| SERS                            | Attaching plasmonic nanoparticles to amplify Raman signal             | Gold nanoparticles                               | Biodistribution in tumors, Multiplexed detection                | Tumor-bearing mice                          | IV      | Unparalleled specificity<br>Very high sensitivity                              | Stability, toxicity<br>Penetration                                 | (78, 79)         |

Edg, Endogenous.

conventional fluorescent labeling methods may alter the active sites of exosomal membrane proteins, and potentially affect their biological functions (22), a novel strategy that integrates azide (N<sub>3</sub>)-containing unnatural choline analogs into exosomes phospholipids has been developed to address this limitation (17). This approach uses DBCO–Cy5 and DBCO–Cy7, which bind to azide-modified phospholipids with high efficiency, enabling bio-orthogonal exosome labeling. This technique demonstrated a differential distribution of exosomes from distinct cell types in brain tissue, and the role of interactions with astrocytes in determining selective exosome tropism. A novel exosome labeling strategy that uses semiconductor polymer dots (Pdts), which emit fluorescence in the NIR–II range, was recently developed to track the *in vivo* biodistribution of MSC-derived exosomes (23). Glucose-coated Pdts showed high labeling efficiency with the biological properties of the MSC-derived exosome. This labeling strategy can be a valuable tool for future investigations of the therapeutic potential of MSC-derived exosomes in liver regenerative medicine.

#### Bioluminescence imaging (BLI)

BLI, which detects visible light emission from luciferase-catalyzed substrate oxidation, is an effective tool for *in vivo* molecular imaging (24). The *firefly* luciferase–luciferin reaction emits light in the (530–640) nm range, with peak emission at 562 nm. Wavelengths above 600 nm experience reduced tissue scattering and absorption, allowing deeper tissue (25). These favorable optical properties, combined with high sensitivity, make BLI a valuable tool for *in vivo* signal quantitative analysis, enabling exosome dynamics and drug distribution monitoring in living organisms. However, BLI has several limitations, its primary limitation being the attenuation of light transmission through tissues. Photon intensity decreases by approximately 10-fold per centimeter of tissue depth, resulting in a significant signal strength reduction in deeper tissues, when compared with surface tissues (26). In addition, since BLI is a surface-weighted technique, light sources closer to the animal surface are bright, while deeper tissue signals are relatively faint. This characteristic limits the detection of deeper tissue physiological changes. To overcome these limitations, advanced luciferase systems, such as *Renilla* luciferase (RLuc) from *Renilla reniformis*, have been introduced for exosome imaging (27). RLuc offers high luminescence efficiency and rapid response time. The luminescent reaction of RLuc does not require oxygen or ATP, and is non-toxic to cells and tissues, making it suited to tracking small molecules like exosomes. A study genetically modified CAL–62 (thyroid cancer) and MDA–MB–468 (breast cancer) cells using lentiviral transfection to express RLuc, ensuring that these cells' exosomes contained the RLuc protein. This study demonstrated effective exosome biodistribution tracking using the RLuc system, suggesting this system is a valuable exosome research tool. An *in vivo* exosome tracking study using BLI reported the use of NanoLuc (NLuc) expressed on the exosome membrane protein

to track exosomes (28). This study showed that the CD63 gene, an exosome surface protein, was fused with the NLuc gene to create the CD63NanoLuc reporter. Expressing the reporter in genetically modified C57/B6 background mice under a heart-specific promoter,  $\alpha$ MHC–STOP–CD63NanoLuc, enabled precise spatiotemporal tracking of endogenous exosome release from cardiomyocytes (29). A similar study aiming to integrate exosome surface proteins with BLI systems proposed a method of monitoring *in vivo* exosome distribution by fusing Antares2, a Bioluminescence Resonance Energy Transfer (BRET)-based luciferase, to CD63 (30). BRET technology works by transferring energy from the luciferase enzyme's emitted light to nearby receptor proteins, resulting in light emission at longer wavelengths. In this study, PC3 (a human prostate cancer cell line expressing CD63–Antares2) cells were tracked *in vivo* for 35 days (31). This study demonstrates that CD63–Antares2 expression enables long-term, quantitative, time-dependent monitoring of cancer-derived exosome circulation *in vivo*. Also, recent hybrid imaging systems combining NIR fluorescence and luciferase-based bioluminescence have been used to enhance resolution and signal sensitivity, allowing deeper tissue penetration and improved real-time imaging. These advanced systems provide critical insights into exosome dynamics, particularly in tumor microenvironments.

#### MAGNETIC RESONANCE IMAGING (MRI)

MRI, which is based on the nuclear magnetic resonance principle, uses strong magnetic fields and radiofrequency pulses to excite hydrogen nuclei in the body, producing high-resolution cross-sectional images (32). This non-invasive imaging technique offers the advantage of safely visualizing internal body structures without using ionizing radiation, while providing a high signal-to-noise ratio and deep tissue penetration (33, 34). However, its low sensitivity makes it challenging to detect weak signals from molecular or cellular-level targets (35). Further, the high cost of maintaining and operating superconducting magnets imposes a significant economic burden on large-scale experimental applications, while prolonged scan times may hinder the real-time tracking of dynamic processes or rapid physiological changes (36, 37). To address these challenges, ongoing research is focusing on developing contrast agents, MRI signal amplification techniques, and faster scanning protocols.

Recent studies leveraging superfluorinated extracellular vesicles for *in vivo* fluorine-19 MRI imaging have attracted significant attention to address conventional MRI limitations (38). This approach involves incorporating perfluorocarbon compounds containing fluorine-19 atoms into the exosome membrane to enhance fluorine signals. An *in vivo* study using C57BL/6 mice detected prominent liver and spleen signals, demonstrating the feasibility of non-invasive, high-resolution, quantitative exosome imaging. Other studies imaging MSC-derived exosomes have used an indirect labeling strategy by using a lentiviral vector to

fuse the MRI reporter gene, ferritin heavy chain (FTH1), to lactadherin, an exosome membrane protein (39). In this study, MSCs were transduced with a lentivirus expressing FTH1 under the control of the cytomegalovirus promoter. This approach provided a non-invasive, high-resolution method of tracing MSC-derived exosomes in C57BL/6 mice. In addition, genetically engineered MRI-traceable exosomes have been used as SARS-CoV-2 mimetics to track ACE2 binding *in vivo* (40). To investigate receptor-binding domain (RBD)-ACE2 interactions, RBD-expressing HEK-293 cells were co-cultured with SPIONs, with this direct labeling approach yielding SPION-labeled exosomes. This study demonstrated the feasibility of real-time *in vivo* RBD-ACE2 interaction tracking using SPION-labeled, RBD-expressing exosomes. Another study showed that MRI-traceable glucose oxidase (GOD)-enzymatic superparamagnetic iron oxide nanoparticles (ESIONs) exosomes were developed as a catalytic-based therapeutic system for hepatocellular carcinoma (HCC) (41); MRI allowed real-time exosome distribution and therapeutic efficacy monitoring, enabling precise, non-invasive HCC treatment progress tracking and evaluation. Recent studies have demonstrated that macrophage-derived exosome-conjugated ESIONPs (ESIONPs@EXO) enable the therapeutic targeting of pathological angiogenesis and non-invasive monitoring via MRI (42), demonstrating that ESIONPs@EXO effectively targets pathological angiogenesis without toxicity, while allowing real-time therapeutic efficacy monitoring using MRI. Recent advances have focused on using exosome membrane-encapsulated SPIONs to enhance MRI contrast. Also, hybrid nanoplateforms that integrate MRI with therapeutic agents have been used for theranostic applications, particularly in cancer treatment. These multifunctional systems provide imaging and therapeutic abilities to allow real-time treatment efficacy and biodistribution monitoring.

Magnetic Particle Imaging (MPI), an emerging, noninvasive tomographic imaging modality, directly measures and tracks the distribution and concentration of SPIONs *in vivo* (43). Because MPI exploits the magnetic moments of SPIONs, which are 22 million times stronger than the nuclear magnetic moments detected by MRI, it provides significantly higher sensitivity and superior tissue penetration, compared to the conventional MRI (44). As well, SPIONs are suitable for long-term tracking because they exhibit high biocompatibility, and compared with traditional imaging methods that use radioactive tracers, MPI offers improved safety (45). To better understand exosome accumulation and localization, recent studies have used MPI to track iron-labeled exosomes (46). A study co-cultured 4T1BR5-L2G cells with SPIONs to indirectly label exosomes with iron. MPI signals only in the mice with brain metastases, demonstrating the effectiveness of MPI in tumor-targeting research using exosomes. MPI-based research using SPION-loaded exosomes has also been conducted in prostate cancer (PCa) models (47). Exosomes derived from the urine of patients with PCa were labeled with SPIONs and fluorescent dyes through sonication and co-incubation, follo-

wed by intravenous injection into an orthotopic PCa mouse model and imaging signal analysis. These results highlight the superior longevity of MPI signals and MPI's advantages over conventional imaging techniques. Collectively, these studies establish MPI as a highly sensitive and long-term imaging modality, with promise as a tool for exosome-based cancer diagnosis and tracking.

## SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)

SPECT imaging is an attractive method for real-time exosome distribution and dynamics monitoring *in vivo* (48). SPECT imaging detects single photons emitted from gamma-ray radionuclides with energies ranging (30-300) keV, and half-lives ranging from hours to days (49). The  $\gamma$ -rays emitted by such radionuclides can be detected using a lead collimator, because of isotropic  $\gamma$ -ray emission from SPECT isotopes (50). However, only a portion of the photons pass through the specified collimator aperture, significantly reducing resolution and sensitivity (51). In addition, the scattering and absorption that occur when  $\gamma$ -rays pass through biological tissues, including denser bone tissues, can distort the signal, which when determining radionuclide distribution in the body, may limit quantitative accuracy (52).

Several studies have demonstrated that SPECT imaging of radiolabeled exosomes can overcome fluorescence imaging shortcomings and allow exosome tracking *in vivo*. In one study, the radionuclide  $^{111}\text{In}$  was chelated to the membrane-permeable 8-hydroxyquinoline (oxine) to form the lipophilic complex,  $^{111}\text{In}$ -oxine, allowing exosomes to be monitored via SPECT *in vivo* (53). In another study, exosomes were labeled via covalent bonding between amine groups on the surface of melanoma exosomes (54). This study demonstrated that the exosome's membrane physiology can be used to achieve stable exosome radionuclide labeling. Another study reported a rapid method to radiolabel exosomes with  $^{99\text{m}}\text{Tc}$  for SPECT-CT imaging *in vivo*.  $^{99\text{m}}\text{Tc}$  was chelated to the lipophilic compound, hexamethylpropyleneamine oxime (HMPAO), and also used to radiolabel exosome-mimetic nanovesicles (55). Using this method, ENVs from murine macrophage Raw 264.7 cells were radiolabeled with  $^{99\text{m}}\text{Tc}$ -HMPAO, and intravenously administered into BALB/c mice. The results demonstrated that the  $^{99\text{m}}\text{Tc}$ -HMPAO-ENVs can provide quantitative, reproducible SPECT images for dynamic exosome and ENV monitoring. Another  $^{99\text{m}}\text{Tc}$ -based exosome imaging strategy used  $^{99\text{m}}\text{Tc}$  chelation to hydrazinonic acid (HYNIC) (56). Tumor-derived exosomes were modified with 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol) 2000]-HYNIC, which could then be radiolabeled with  $\text{Tc-}^{99\text{m}}$ , allowing visualization *in vivo*. Using this strategy,  $^{99\text{m}}\text{Tc}$ -labeled exosomes from human colon cancer cell line HCT 116 were intravenously administered into tumor-bearing mice. These results showed that modified tumor-derived exo-

somes can be monitored as a multi-modular nanocarrier for SPECT imaging *in vivo*. In a recent study, HER2-targeting exosomes extracted from HEK293T cells co-expressing lysosome-associated membrane protein 2b's extracellular domain and designed ankyrin repeat proteins were radiolabeled using  $\text{fac-}[^{99\text{m}}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$  synthon (57). The accumulation of  $^{99\text{m}}\text{Tc}$ -exosomes in the high HER2 expression tumor suggested that these exosomes interact through specific targeting, thereby highlighting the potential of using SPECT imaging. A relatively simple method of oxidizing iodine-131 to the tyrosine residues of exosome membrane proteins can be used for dynamic exosome monitoring *in vivo* (58); in this method, dynamic exosome monitoring *in vivo* using SPECT/CT confirmed that the exosomes isolated from myeloid-derived suppressor cells and endothelial progenitor cells accumulated in the primary breast tumor site. Therefore, combined with SPECT imaging, simple radionuclide labeling methods may elucidate the potential of exosome imaging and quantification in diagnosis, as well as the effectiveness of exosome-based therapy. Hybrid SPECT imaging systems combining radionuclide labeling with fluorescent dyes have also been developed. This dual-mode imaging approach enhances spatial resolution, while allowing simultaneous anatomical and functional analysis of exosome dynamics. Recent studies using  $^{111}\text{In}$ -labeled exosomes in cancer models have demonstrated their utility in visualizing tumor-targeting properties and evaluating therapeutic efficacy.

## POSITRON EMISSION TOMOGRAPHY (PET)

PET, a highly sensitive molecular imaging technique, uses positron-emitting radionuclide-labeled probes to visualize and quantify biological processes *in vivo* (59). PET imaging is based on detecting two 511 keV annihilation photons, which, when a positron from a radionuclide undergoes annihilation after colliding with an electron, are emitted in opposite directions (60). By offering picomolar-level sensitivity, this imaging strategy enables molecular probe detection and quantitative molecular and functional change analysis *in vivo* (61). Also, PET provides greater tissue penetration depth than other imaging modalities, allowing labeled probes to be effectively monitored within the body (62). However, the short half-life of PET radionuclides constrains radiotracer synthesis and imaging time, potentially reducing *in vivo* imaging accuracy (63). Furthermore, PET imaging requires cyclotron-produced radionuclides, which may limit its accessibility and widespread application (64). To overcome these limitations, alternative PET imaging strategies that use radionuclides with longer half-lives have been explored. Moreover, to enhance PET's capabilities by reducing non-specific signals and improving the reliability of imaging results, multimodal imaging approaches like simultaneous PET/MRI have been developed (65).

For effective *in vivo* exosome imaging, it is essential to use radionuclides with relatively long half-lives, and to establish a

stable and specific exosome-labeling strategy. Because of its relatively long half-life (78.4 h), the radionuclide, zirconium-89 ( $^{89}\text{Zr}$ ), is suitable for PET imaging. Labeling exosomes with  $^{89}\text{Zr}$  enables long-term tracking, and overcomes PET's short imaging duration limitations (66). In this study, desferrioxamine, a siderophore-based chelator, was used to label exosomes. PET imaging showed rapid  $^{89}\text{Zr}$ -exo accumulation in the liver and spleen; and interestingly, in the thyroid and gonads. Other exosome surface radioactive isotope labeling strategies have been explored, mainly using the positron-emitting isotope, copper-64 ( $^{64}\text{Cu}$ ) (67). Exosomes isolated from human osteosarcoma 143B cells were labeled with  $^{64}\text{Cu}$ -NODAGA ( $^{64}\text{Cu}$ -NODAGA-EXs), and intravenously injected into Foxn1nu nude mice. PET/MRI imaging analysis revealed strong  $^{64}\text{Cu}$ -NODAGA-EXs accumulation in the kidneys 24 h post-injection, with relatively low signals being detected in other organs, including the liver and spleen. This study shows that labeling exosome surfaces with  $^{64}\text{Cu}$  can preserve their disease-targeting ability, while adding molecular imaging functionality using radioactive isotopes. Advances in exosome-based drug delivery are also closely linked to improving exosome accessibility at specific sites within the body. Consequently, strategies for labeling exosomes with radionuclides and enhancing their tumor-targeting ability *in vivo* have been actively investigated (68). In this study, 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) was conjugated to exosomes to enable the formation of a stable coordination bond with  $^{64}\text{Cu}$ , facilitating radionuclide labeling. Exosomes derived from mouse triple-negative breast cancer cells (4T1) were labeled with  $^{64}\text{Cu}$ -NOTA and PEG, forming  $^{64}\text{Cu}$ -NOTA-Exosome-PEG. PET imaging revealed that the tumor accumulation of PEGylated exosomes was approximately three times higher than that of non-PEGylated exosomes. This finding indicates that PEGylation enhances the permeability and retention effect, reducing hepatic clearance and improving exosome pharmacokinetics *in vivo*. PET imaging innovations have focused on developing exosome-targeted radiotracers, such as  $^{89}\text{Zr}$  and  $^{64}\text{Cu}$ , conjugated with exosome surface proteins. These advanced radiotracers allow high-resolution exosome tracking *in vivo*, while providing insights into their biodistribution and interaction with tumor microenvironments. As well, hybrid PET/MRI systems combining radiotracers and magnetic nanoparticles have been explored for their multimodal imaging and enhanced diagnostic accuracy potential.

## OTHER IMAGING STRATEGIES

Although various imaging techniques, including optical imaging, MRI, SPECT, and PET, have been used for exosome tracking *in vivo*, they all display limitations of sensitivity, resolution, and tissue penetration, necessitating new imaging strategies. Photoacoustic imaging (PAI) is an emerging non-invasive imaging technology that combines the high tissue penetration of ultrasound imaging with the excellent speci-

ficity of optical imaging. This technique uses short-pulsed light sources, such as lasers, to induce thermoelastic expansion when specific molecules in tissues absorb the light, generating ultrasound waves that are detected to produce high-resolution images (69, 70). Compared to conventional imaging, PAI enables deeper tissue analysis, and offers advantages that include lack of radiation exposure, rapid imaging, and cost-effectiveness (71). Recent research using PAI has focused on targeted glioblastoma detection and treatment using exosomes derived from U-87 cells. In this study, exosomes were hybridized with Prussian blue nanoparticles (PBNPs), followed by coating via an extrusion method to develop a hybrid nanostructure (Exo:PB) (72). When intravenously administered into an orthotopic mouse glioblastoma model, strong PBNP signals were observed in the brain region. This study suggests that PAI-based imaging using an exosome-based nanoplatform has potential future applications in precise cancer diagnosis and therapy.

Ultrasound imaging, a non-invasive and real-time imaging modality, has emerged as a promising exosome tracking technique. Conjugating exosomes with microbubbles, which are commonly used as ultrasound contrast agents, can enhance their visualization and provide insights into their biodistribution. Combining exosomes with microbubbles improves signal contrast, and facilitates targeted therapeutic agent delivery (73). Recent studies have demonstrated the successful use of microbubble-conjugated exosomes to target tumors *in vivo*, thereby providing valuable information about their migration patterns and accumulation in specific tissues (74). Also, because ultrasound imaging is cost-effective and scalable, it provides a viable preclinical and clinical research option. However, optimizing exosome-microbubble conjugate stability and functional integrity during imaging is challenging. Future advances in the development of more stable and biocompatible microbubble formulations are expected to overcome these limitations, and expand ultrasound-based exosome imaging applications.

Surface-enhanced Raman spectroscopy (SERS) is a technique that amplifies Raman signals generated by the inelastic scattering of molecules by several orders of magnitude near metallic nanostructure surfaces (75, 76). This enhancement is primarily driven by the electromagnetic effect resulting from surface plasmon resonance in metal nanoparticles. Due to its high sensitivity, non-invasive nature, and ability to provide molecular-level fingerprint information, SERS is well-suited to exosome labeling and detection using plasmonic nanoparticles, enabling the identification of even trace amounts of exosomes (77). A recent study demonstrated that SERS-based gold nanoparticle labeling enables both highly sensitive detection of exosomes via a sandwich-type immunoassay, and *in vivo* monitoring of their biodistribution, revealing specific accumulation patterns in tumor microenvironments (78). Another study introduced a multiplexed SERS detection strategy combining aptamer-modified gold shell magnetic beads and

Raman reporter-conjugated gold nanoparticles to enable simultaneous screening of multiple cancer-derived exosomes. By targeting the generic exosomal marker CD63 and specific tumor-related epitopes, this platform successfully detected distinct exosome subtypes in both buffer and human blood samples, highlighting its potential in clinical cancer diagnostics and early screening applications (79). Although SERS offers unparalleled specificity and sensitivity, its *in vivo* application is limited by such challenges as nanoparticle stability and potential toxicity. To mitigate these challenges and enhance the clinical feasibility of Raman-based exosome imaging, ongoing research is focusing on developing biocompatible SERS substrates.

## CONCLUSION

This review highlights the critical role of advanced imaging technologies in enhancing understanding of exosome biodistribution, dynamics, and clinical potential. To address this need, numerous molecular imaging strategies have been established, with a comprehensive overview provided (Table 1). We have summarized various modalities, including optical imaging, MRI, SPECT, and PET, each of which presents a unique balance of advantages and disadvantages. Optical imaging, while highly sensitive for preclinical real-time tracking, is constrained by limited tissue penetration. Conversely, MRI and nuclear imaging (SPECT/PET) are well-established in clinical settings, and offer superior penetration depth and anatomical resolution or sensitivity, respectively. However, the inherent low sensitivity of MRI necessitates the development of advanced contrast agents, while nuclear imaging faces challenges related to the short half-lives of radionuclides and regulatory hurdles for clinical use. Among the imaging modalities discussed, PET and PET/MRI hybrid systems show the greatest potential for clinical translation, due to their high sensitivity, quantitative capability, and suitability for deep tissue tracking. Furthermore, emerging techniques, such as magnetic particle imaging (MPI), photoacoustic imaging (PAI), and surface-enhanced Raman spectroscopy (SERS), offer new avenues for precise and multimodal exosome tracking. These modalities, especially when combined with therapeutic payloads or integrated into theranostic platforms, represent promising directions for future clinical application. Despite these advances, the interpretation of exosome imaging data requires careful consideration of limitations in commonly used labeling strategies. For example, non-specific signals from free probes, dye-induced exosome aggregation, or unintended alterations in membrane protein function may lead to artifacts or misrepresentation of biological activity (80). Standardizing labeling protocols and developing safer, more stable probes will be critical to ensure reproducibility and reliability. Furthermore, the integration of artificial intelligence (AI) and computational tools in these exosome imaging techniques will be transformative. AI-driven algorithms can significantly enhance image

analysis by improving signal-to-noise ratios, automating the segmentation of target tissues, and enabling complex quantitative analysis of exosome trafficking dynamics from large datasets. Also, predictive models could correlate imaging-derived biodistribution patterns with therapeutic efficacy, providing a forward-looking perspective for personalized medicine.

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## CONFLICTS OF INTEREST

The authors have no conflicting interests.

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