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Multimodality Imaging Agents with PET as the Fundamental Pillar

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Abstract

Positron emission tomography (PET) provides quantitative information *in vivo* with ultra-high sensitivity but is limited by its relatively low spatial resolution. Therefore, PET has been combined with other imaging modalities, and commercial systems such as PET/computed tomography (CT) and PET/magnetic resonance (MR) have become available. Inspired by the emerging field of nanomedicine, many PET-based multimodality nanoparticle imaging agents have been developed in recent years. This Minireview highlights recent progress in the design of PET-based dual-modality and tri-or-more modality imaging nanoprobe with an aim to overview the major advances and key challenges in this field and substantially improve our knowledge of this fertile research area.

Keywords

PET; imaging agents; nanomedicine; dual-modality imaging; multimodality imaging

1. Introduction

Over the years, rapid development of noninvasive imaging modalities has offered tremendous opportunities for disease diagnosis and therapeutic intervention, through the use of positron emission tomography (PET) and single photon emission computed tomography (SPECT), magnetic resonance (MR) imaging, optical imaging, X-ray computed tomography (CT), and others.^[1] With its extremely high detection sensitivity (10^{-11} to 10^{-12} M), quantification capability, and unlimited depth penetration, PET has been applied in various ways to assist in early lesion detection, tracking of biomarkers, drug development, and individualized treatment optimization.^[2] However, PET has intrinsic limitations, such as insufficient spatial resolution, which makes it difficult to obtain comprehensive information about disease sites and cannot be overcome by improving imaging instrumentation alone. To compensate for this problem, the combination of imaging modalities, such as PET/CT or PET/MR, has been proposed, where PET offers functional information about the disease and MR or CT provides high-resolution images for anatomical information.^[3]

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The first commercial installation of a fused PET/CT instrument in 2001 and PET/MR in 2010 instills great confidence in exploiting PET-based multimodality imaging probes and has accelerated the development of this field tremendously.^[4] Since then a significant amount of effort has been devoted to design and develop nanoparticles (NPs) as multimodal imaging probes,^[5] combining PET with at least one other imaging modality such as MR, optical, photoacoustic (PA), and so on.^[6] The unique physicochemical and biological properties of NPs and their surface versatility provide these radioactive imaging nanoprobes with great potential as innovative diagnostic agents.^[6b, 7] In 2014, the first-in-human trial of Cornell dots (C dots) by Bradbury and co-workers represented the first application of multimodality imaging NPs in humans, providing confidence for the future development of PET-based multimodality imaging nanoprobes.^[8] Recently, PET-based tri-modality, tetra-modality, and even hexa-modality imaging nanoprobes have been successfully designed.^[9]

Since each imaging modality has its specific strengths and weaknesses (as seen in Figure 1) and multimodality imaging can provide a multitude of functional and anatomical imaging information, it is necessary to have a proper understanding of the involved processes and issues in the engineering of PET-based multimodality nanoprobes. In this Minireview, we therefore summarize the properties, hybrid imaging types, biomedical applications, and clinical translation potential of these multimodality imaging nanoprobes. We hope that this Minireview will raise extensive interest and call for broad collaboration among experts in chemistry, physics, engineering, and biology to advance the development of multimodality imaging in both preclinical and clinical trials.

2. PET as a perfect partner for dual-modality imaging

One of the most commonly used strategies for synthesizing PET-based dual-modality nanoprobes is chelator-free or chelator-based radiolabeling of NPs that exhibit intrinsic imaging abilities,^[7c, 10] such as magnetic NPs for PET/MR, quantum dots (QDs) or upconversion nanoparticles (UCNPs) for PET/optical, or gold NPs for PET/PA imaging. Also, isotopes and other imaging agents can be integrated into the interior or on the surface of traditional organic NPs (e.g., micelles, liposomes, dendrimers, and polymeric NPs). Logically, the choice of an imaging modality to combine with PET should avoid overlap of advantages and compensate for the weakness of each individual modality to obtain synergistic imaging. For example, imaging agents for combining PET with CT or ultrasound imaging have been rarely reported. CT has very low sensitivity and the large disparity in the concentrations of contrast agents needed for PET and contrast-enhanced CT led to few researchers focusing on synthesizing PET/CT nanoprobes.^[11] Therefore, CT images are usually used to visualize the anatomic location of PET tracer uptake within the body. Ultrasound imaging agents are mostly based on micro bubbles, and there have been very few studies on PET/ultrasound dual-modality imaging to date. So far, most efforts have been devoted to designing dual-modality nanoprobes for PET/MR, PET/optical, and PET/PA imaging systems.

2.1. PET/MR imaging

The idea of combining PET and MR was presented even before PET/CT,^[12] with the first PET/MR systems connecting individual PET and MR scanners by a table.^[13] Currently, fully integrated PET/MR scanners are commercially available and are commonly used clinically. Such dual-modality imaging systems benefit from the high anatomical spatial resolution and exquisite soft tissue contrast of MR and the highly sensitive functional imaging of PET. So far, dual-modality PET/MR nanoprobes are typically synthesized by radiolabeling classical MR contrast agents (CAs), including iron oxide NPs (IONPs) for T_2 -weighted PET/MR dual-modality imaging, and gadolinium or manganese-based NPs for T_1 -weighted PET/MR dual-modality imaging.^[14]

2.1.1. PET/ T_2 -MR imaging—IONPs act as CAs to shorten the transverse (T_2) relaxation time of nearby water molecules, resulting in negative contrast enhancement (darker image) in T_2 -weighted MR imaging.^[14] Since the pioneer work of PET/MR dual-modality imaging of tumor integrin expression using ^{64}Cu -labeled and arginine-glycine-aspartic (RGD)-conjugated IONPs,^[15] much work has been focused on radiolabeling IONPs with various isotopes, including short-lived isotopes such as ^{11}C ($t_{1/2}$ = 20.4 minutes)^[16], ^{68}Ga ($t_{1/2}$ =67.7 minutes)^[17], and ^{18}F ($t_{1/2}$ =109.8 minutes)^[18], and longer-lived isotopes such as ^{64}Cu ($t_{1/2}$ =12.7 h)^[19], ^{72}As ($t_{1/2}$ =26 h)^[20], ^{69}Ge ($t_{1/2}$ =39.05 h)^[21], ^{89}Zr ($t_{1/2}$ =78.4 h)^[22], and ^{124}I ($t_{1/2}$ =4.2 days).^[23]

Traditional radiolabeling strategies involve conjugating the polymeric surface coatings of IONPs with chelators such as DFO (desferrioxamine B) for ^{89}Zr coordination,^[22] tyrosine residues for ^{124}I binding,^[23] and DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) for ^{64}Cu chelation.^[15, 19f, 19g] For example, Grimm and co-workers bound ^{89}Zr to magnetic ferumoxytol using DFO as a chelator to construct PET/ T_2 -MR dual-modality nanoprobes (Figure 2a),^[22] which allowed for high-sensitivity and high-resolution delineation and resection of deep-tissue nodes in axillary drainage models.

To simplify the radiolabeling procedure and explore faster and more general radiolabeling possibilities, much attention has been paid to develop more reliable radiolabeling routes without using chelators. Usually, three strategies are used to radiolabel IONPs in a chelator-free manner: (i) doping radioactive ions into magnetic NPs; (ii) coating NPs with materials that have high affinity for specific isotopes; and (iii) exploiting the strong binding affinity between isotopes and certain NPs. For example, ^{68}Ga , ^{59}Fe , and ^{64}Cu have been directly doped into the lattice of iron oxide NPs,^[17b, 17c, 24] and the resulting NPs demonstrated high radiolabeling stability for PET imaging and could modulate MRI relaxivity simultaneously.^[17b, 19a] In another study, the surface of magnetic MnFe_2O_4 NPs was coated with biocompatible aluminum hydroxide for direct ^{18}F binding,^[18] since this coating displays a high affinity for fluoride ions. Due to the strong binding affinity of arsenic and germanium ions for metal oxides, our group developed a simple but highly efficient strategy to intrinsically label radioactive ^{69}Ge and ^{72}As (*= 71, 72, 74, 76) on the surface of superparamagnetic iron oxide NPs (SPIONs).^[20–21] As a proof-of-concept, these PET/MR dual-modality nanoprobes showed great potential for sentinel lymph node mapping, offering

quantitative information (from the PET imaging) while achieving high soft-tissue contrast by MR imaging at the same time (Figure 2b-e).

2.1.2. PET/ T_1 -MR imaging—Since the most frequently used CAs clinically are paramagnetic complexes (usually Gd^{3+} or Mn^{2+} chelates) that shorten the longitudinal (T_1) relaxation time of water and obtain a positive contrast enhancement (brighter image) in T_1 -weighted MR imaging, radiolabeling Gd/Mn-based NPs is a preferred choice for constructing PET/MR dual-modality imaging nanoprobe. To date, many types of T_1 CAs have been radiolabeled to develop PET/MR agents, including $Gd_3N@C80$ NPs,^[25] $GdVO_4$:Eu nanosheets,^[26] Gd^{3+} -containing polymeric NPs,^[27] MnO NPs,^[28] and Mn_3O_4 NPs.^[29] Based on the electrostatic interactions between nanopores and metal ions, Kaittanis *et al.* developed multifunctional PET/ T_1 -MR imaging nanobeacons for sentinel lymph node detection using glucose-based polymeric dextran nanomaterials to retain both ^{89}Zr and Gd^{3+} metal ions.^[27b] In another study, Gd^{3+} ions were caged inside fullerene nanostructures to avoid Gd^{3+} leakage and followed by ^{124}I labeling (^{124}I -labeled $Gd_3N@C80$),^[25] and these structures could be used to distinctly visualize glioblastoma inside the brain of rats by both T_1 -MR imaging and PET imaging.

PET/ T_1 -MR dual-modality imaging is usually applied for tumor diagnosis. Actively-targeted PET/MR tumor imaging was realized by conjugating these agents with targeted ligands, including Octreotide,^[27c] RGD,^[30] TRC105,^[29] and folic acid.^[31] Recently, by conjugating Mn_3O_4 NPs with ^{64}Cu and TRC105 as the targeting ligand for CD105, our group presented tumor vasculature-targeted PET/ T_1 -MR dual-modality imaging in tumor-bearing mice (Figure 3a).^[29] Dual-modal PET/MR imaging showed that the synthesized nanoprobe accumulated in tumor sites rapidly, peaking at 6 h p.i. and remaining stable over time. For passively-targeted imaging through the well-known enhanced permeability and retention (EPR) effect, ^{64}Cu was labeled to human serum albumin-coated MnO NPs using DOTA as the chelator.^[28] PET imaging revealed that tumor accumulation of ^{64}Cu - MnO NPs peaked at 4 h p.i. (~4.7 %ID/g), and slightly decreased to ~4.3 %ID/g at 24 h, which correlated well with the observation from T_1 -MR imaging (Figure 3b-c).

2.2. PET/optical imaging

The development of PET/optical dual-modality molecular imaging agents has received particular attention for potential clinical translation. Such combined contrast agents would enable whole-body imaging with PET and subsequent multispectral detection or intraoperative applications (e.g., surgical intervention with an intraoperative optical imaging system).

2.2.1 PET/fluorescence imaging—One common strategy to construct dual-modality imaging agents for PET/optical imaging is radiolabeling fluorescence-emitting NPs (e.g., QDs,^[32] ZnO NPs,^[33] UCNPs,^[34] etc.). For example, QDs with narrow emission bands tunable from the ultraviolet (UV) to the near-infrared (NIR) regions have been radiolabeled with ^{18}F or ^{64}Cu ,^[32] allowing PET/optical dual-modality *in vivo* imaging from the subcellular scale to the whole body. Another widely-used strategy involves integrating isotopes and fluorescent dyes into the nanoscale matrix of NPs, such as organic polymeric

NPs,^[35] inorganic silica-based NPs,^[36] iron oxide NPs,^[37] and ferritin nanocages (Figure 4a).^[38] For example, Zheng and coworkers introduced chelator-free porphyrins that have an intrinsic capacity for ⁶⁴Cu radiolabeling to achieve PET/fluorescence imaging of orthotopic prostate cancer.^[35b] Using the fluorescent dye chlorin e6 as a ⁶⁴Cu chelating agent, we recently designed PET/fluorescence dual-modality nanomicelles and imaging results from both modalities revealed that the nanomicelles displayed high tumor uptake ($13.7 \pm 2.2\%$ ID/g).^[35a]

A representative inorganic PET/optical dual-modality imaging nanoprobe is the C dot which is composed of an ultra-small dense SiO₂ core with an inherent fluorescent dye (Cy5) for fluorescence imaging and ¹²⁴I radiolabeling for PET imaging (Figure 4b).^[40] Importantly, silica offers a chemically stable vehicle for the protection of encapsulated dyes from external perturbations. By combining key benefits of PET with those of deep-red/NIR optical imaging, tumor-selective targeting, nodal mapping studies, and intraoperative image-guided metastatic disease detection using these PET/optical dual-modality agents were successfully demonstrated in both small (mouse) and large (miniswine) animal melanoma models.^[8a] Furthermore, as the first-in-human clinical study of PET/optical dual-modal nanoprobe, these ultra-small C dots exhibited preferential renal clearance, excellent biocompatibility, and specific tumor accumulation in metastatic melanoma patients, showing great potential towards clinical translation.^[8b]

2.2.2. PET/Cerenkov luminescence imaging—In recent years, there has been increasing interest in utilizing Cerenkov luminescence (CL) from radiolabeled NPs,^[39] which is produced when charged particles (e.g., β particles) travel in a faster phase velocity than that of light in a particular medium. With only radiolabeling, both PET and optical imaging can be realized and no external light excitation is required. As a result, PET/CL dual-modality imaging could be applied to track the *in vivo* fate of degradable NPs for lung gene transfer imaging, where CL could be acquired using a standard IVIS system that expanded imaging accessibility and the possibilities for high throughput screening.^[41] However, CL is more intense at higher frequencies (UV/blue), which can be easily attenuated by tissues. Fortunately, various NPs including QDs,^[42] TiO₂ NPs,^[43] Au NPs,^[44] and rare-earth NPs,^[45] can be excited by the UV/blue Cerenkov luminescence of labeled isotopes, and then in turn emit a longer wavelength of light that allows for much greater depth penetration (Figure 4c). This phenomenon is known as Cerenkov resonance energy transfer (CRET). For example, Chen and co-workers developed PET/CRET imaging nanoprobe by incorporating ⁶⁴Cu into CdSe/ZnS NPs^[42b] or CuInS/ZnS NPs.^[42a] Both PET and CRET luminescence were successfully applied for *in vivo* tumor imaging. In another recent study, Grimm and co-workers systematically studied the interactions between radionuclides and various NPs and explored novel NP-based multimodality imaging methods.^[46]

2.2.3. PET/Raman imaging—Raman imaging enabled by the surface-enhanced Raman scattering (SERS) effect allows for highly sensitive and specific identification of SERS CAs due to the unique signatures of SERS spectra. SERS NPs have been reported to serve as multimodality imaging platforms in living subjects, particularly for guidance of

intraoperative brain tumor resection.^[47] Radiolabeled SERS NPs can be used for PET/Raman dual-modality imaging, enabling whole-body imaging with PET as a pre-operative roadmap and subsequent precision guidance with a Raman imaging device or handheld Raman scanner during surgical procedures. By conjugating ⁶⁴Cu to the surface of SERS gold NPs, Gambhir and co-workers assessed the natural biodistribution of SERS gold NPs using PET followed by Raman imaging of removed tissues for confirmation of their localization, finding that Raman imaging of excised tissues correlated well with the distribution data from PET.^[48] In a recent study, the short-lived PET nuclide ⁶⁸Ga was labeled without a chelator to SERS NPs and the utility of these PET/Raman dual-modality NPs was demonstrated in several proof-of-concept studies including lymph node tracking, intraoperative guidance for lymph node resection, and cancer imaging after intravenous injection.^[49]

2.3. PET/PA imaging

PA imaging has deeper tissue penetration than other optical methods and combines the advantages of high resolution of ultrasonic imaging and high sensitivity of optical imaging. Various kinds of nanomaterials (e.g., semiconducting polymer NPs, sulfides, gold nanomaterials, carbon-based nanomaterials, etc.) have been designed for PA imaging of reactive oxygen species, enzyme activity, pH value, and bacterial infection.^[51] So far, inorganic nanomaterials such as CuS NPs,^[52] Au nanotripods,^[53] nanographene,^[54] and organic nanomaterials including melanin NPs,^[55] semiconducting perylene diimide NPs,^[56] and naphthalocyanine micelles (called nanonaps),^[50] have been successfully radiolabeled with ⁶⁴Cu to realize PET/PA dual-modality imaging. PET and PA intrinsically image different things – PA imaging detects the nanomaterials themselves while PET monitors the attached radionuclides. Therefore, PET imaging is usually used to investigate the circulation, biodistribution, and clearance of nanomaterials in detail while PA imaging is performed to confirm tissue specific accumulation of nanomaterials that is observed in PET imaging.^[54]

Lovell and co-workers performed PA gut imaging using nanonaps and provided real-time mapping of intestinal anatomy, pathology and function (Figure 5a-c),^[50] followed by ⁶⁴Cu radiolabeling for PET whole-body imaging with full tissue penetration to monitor the movement of nanonaps through the gastrointestinal tract (Figure 5d-e). Because PET has no tissue penetration limits, serial whole-body coronal slices of the mouse could be obtained (Figure 5f). The localized PA imaging was found to compensate for the spatial resolution limitations of PET imaging.

3. Tri-or-more modality imaging agents with PET

Much attention has also been focused on developing PET-based multimodality imaging agents that enable not only dual-modality, but also tri-or-more modality medical imaging capabilities. To achieve this goal, nanomaterials are usually engineered in a core/shell architecture or a hybrid structure to embrace more imaging capacity from different components. These multimodality imaging agents are often based upon a functional matrix with inherent imaging capabilities (such as an optical or magnetic nanoparticle) or other matrices which are easily engineered on the nanoscale (e.g., silica NPs).^[57]

3.1. Multimodality imaging agents based on magnetic matrices

Radiolabeled magnetic NPs have been reported as matrices to construct hetero-nanostructures in combination with other imaging agents to realize PET/MR-based multimodality imaging, such as Bi₂Se₃ nanosheets for CT,^[9b] MoS₂^[60] or graphene^[61] nanosheets for PA imaging, and UCNPs^[58] or Au NPs^[59] for optical imaging (Figure 6a-c). For example, we recently decorated Bi₂Se₃ nanosheets with FeSe₂ NPs (FeSe₂/Bi₂Se₃) and radiolabeled them with ⁶⁴Cu for PET/MR/CT/PA tetra-modal imaging,^[9b] by taking advantages of the high *r*₂ relaxivity of FeSe₂, the x-ray attenuation of Bi₂Se₃, and the strong NIR optical absorbance of the whole nanostructure (Figure 6d). Unlike the aforementioned approach, Xie *et al.* modified the surface of IONPs with ⁶⁴Cu and fluorescent dye Cy5.5, and PET/MR/fluorescence tri-modality imaging was carefully conducted to investigate the *in vivo* behavior of the nanostructures.^[62] Another facile preparation method for PET/MR/optical multimodality nanoprobe involves radiolabeling *T*₂ contrast agents, such as SPIONs, with radionuclides for PET/MR/CL imaging. For example, ⁶⁸Ga or ¹²⁴I has been labeled to SPIONs to visualize the sentinel lymph nodes on PET/MR/CL images.^[63] Additionally, the generated Cherenkov light from ⁶⁸Ga or ¹²⁴I-SPIONs is also useful for optical surgical guidance.

3.2. Multimodality imaging agents based on optical matrices

UCNPs, a typical representation of inorganic NPs with optical properties, have been widely applied in optical imaging as well as PET-based multimodal imaging. For example, Li and co-workers developed ¹⁸F-labeled NaYF₄-based UCNPs through a facile inorganic reaction based on the strong binding between Y³⁺ and F⁻.^[64] With such a simple nanostructure, they successfully realized *in vivo* upconversion luminescence (UCL) imaging through laser excitation of the UCNPs, contrast-enhanced MR imaging by doping Gd³⁺ into the UCNP matrix, and PET imaging with the labeled ¹⁸F. In another study, NaGdF₄-based UCNPs were radiolabeled with ¹²⁴I and functionalized with RGD peptides to develop multimodal PET/MR/optical nanoprobe for targeting tumor angiogenesis.^[65] Recently, Rieffel *et al.* coated porphyrin-phospholipid (PoP) on the surface of UCNPs and radiolabeled ⁶⁴Cu by exploiting the affinity between copper and porphyrins (Figure 7a-b). The designed ⁶⁴Cu-PoP-UCNPs could realize hexa-modality lymphatic imaging *in vivo*: UCL/CT (by UCNPs), fluorescence imaging/PA (by surface PoP), and PET/CL (by ⁶⁴Cu) (Figure 7c). Their results show that engineering simple, yet higher-order multi-modality imaging agents is feasible and they also shed light on future directions for the development of hyper-integrated imaging nanoprobe systems.

When compared with inorganic NPs, organic optical NPs have generated considerable interest due to their increased biocompatibility, and many such platforms have been developed, including nanoporphyrin,^[9d] melanin NPs,^[66] and coordination polymer NPs.^[67] Considering the special properties of melanin, Cheng and co-workers developed ultra-small (<10 nm) water-soluble melanin NPs (MNPs), which showed unique photoacoustic properties for PA imaging and natural binding with ⁶⁴Cu for PET imaging and Fe³⁺ for enhanced MRI (Figure 7d).^[66] Tumor PET/MR/PA multimodality imaging was demonstrated in U87MG tumors with RGD peptide-functionalized MNPs, allowing for imaging diseases at different depths with molecular and anatomical information. Using a

similar strategy, a highly versatile ‘all-in-one’ fluorescence-emitting nanoporphyrin was developed with the intrinsic ability to chelate metal ions (e.g., $^{64}\text{Cu}^{2+}$, Gd^{3+}) for PET/MR/optical multimodality detection of tumors.^[9d] Importantly, these nanoporphyrins were made based on a single and well-defined building block, which can be easily scaled up to the kilogram level at relatively low cost, providing great potential for clinical translation.

3.3. Multimodality imaging agents based on silica matrices

One major challenge of PET-based multimodality imaging agents is to find an appropriate nanoplatform to load various imaging components together while maintaining their original functions or enhancing their individual imaging performances. With their tunable mesoporous structure and large pore volume, mesoporous silica NPs (MSNs) have been used to load the NIR dye ZW800 and have been labeled with Gd^{3+} (for T_1 -MR imaging) and ^{64}Cu (for PET) through chelation reactions.^[68] Longitudinal PET/MR/optical tri-modal imaging was subsequently achieved to visualize tumor draining sentinel lymph nodes up to 3 weeks after injection imaging nanoprobes in a metastatic 4T1 tumor model. To further improve dye loading, we recently filled porphyrin dyes into hollow mesoporous silica NPs (HMSNs) and radiolabeled them with ^{89}Zr to simultaneously realize PET/fluorescence/CL/CRET tetra-modal imaging for rapid and accurate delineation of tumors.^[9a] Furthermore, by self-assembling ultra-small copper sulfide NPs on the surface of ^{89}Zr -HMSNs, tetra-modality imaging-guided synergistic tumor PDT, and PTT were successfully realized with such hybrid core-satellite nanostructures.

4. Conclusion and outlook

Multimodality imaging with PET can provide both structural and functional information, allowing for accurate and precise assessment of biological processes and thus paving the path towards personalized medicine. The design and synthesis of radioactive nanoprobes are highly promising and desirable for realizing novel cancer management in a PET-based multimodality imaging system. This Minireview details the recent progress in the emerging field of imaging agents for PET-related multimodal imaging, including dual-modality imaging such as PET/MR (T_1 or T_2), PET/optical, and PET/PA imaging, and tri-or-more modality imaging integrated with PET.

While significant promise has been noted with multimodal nanoprobes to date, their full implementation is still in the early stages. As with all nano-related agents, safety and reproducibility issues are of utmost concern. Nanoparticles, along with their many imaging moieties and other components, must be characterized fully and validated in appropriate models. Robust and reproducible synthesis protocols are prerequisite to clinical implementation, and the proper preclinical models (along with controls) are necessary for a full understanding of the *in vivo* behavior of nanoplatforms. Also, future research should explore the different requirements of contrast agents for various imaging modalities and how to account for these in the rational design of a multimodality imaging platform. For instance, the sensitivities of MR and PET are quite different; thus, the amounts of contrast agents required for each are similarly not the same. This disparity could be reconciled through both chelator-based and chelator-free radiolabeling, but only to a certain extent, and this approach

cannot fully account for the several orders of magnitude difference in sensitivity. Therefore, nanoplateforms will have to be uniquely designed in order for proper amounts of the agents for each imaging modality to be delivered to the target tissues.

If a multimodality nanoplateform is able to satisfy these requirements, the benefits for imaging would be great. As imaging technologies advance, the need for more advanced contrast agents will also grow. Nanoparticles are uniquely suited to fill this void, as they are able to incorporate a large number of imaging agents into a single platform in a stable manner. The current clinical translation process of PET/optical dual-modality C dots (NCT01266096 and NCT02106598) may extend to other types of PET-based multimodality imaging agents (e.g., PET/MR) in the future. Certainly, we expect the engineering of PET-based multimodality nanoparticle imaging agents to have an impact on clinical care for a wide variety of diseases in the near future.

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Biography

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Emily B. Ehlerding received her M.S. degree from UW - Madison in 2016, and her B.S. degree from Manchester University in 2014. She is currently a Ph.D. candidate at UW - Madison, working with antibody-based platforms for multimodality imaging of immunotherapy - related targets.

Weibo Cai received his Ph.D. degree from University of California at San Diego in 2004 and is now a Professor at the UW - Madison (<http://mi.wisc.edu>). His research is primarily focused on molecular imaging and nanotechnology, investigating the biomedical applications of various agents developed in his laboratory for imaging and therapy of various diseases.

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Figure 1.
Features of the main imaging modalities described in this Minireview.

Figure 2.

a) Schematic illustration of chelator-based radiolabeling of IONPs with ^{89}Zr using DFO as a chelator. Reproduced with permission from Ref. [22]. Copyright 2014, Nature Publishing Group. b) Schematic illustration of the chelator-free synthesis of $^*\text{As}$ (or ^{69}Ge)-SPIONs. TEM images of SPIONs c) before and d) after transferring them into hydrophilic solutions. e) *In vivo* lymph node PET imaging with $^*\text{As}$ -SPION and T_2 -MRI with SPIONs. Reproduced with permission from Ref. [20]. Copyright 2013, Wiley-VCH.

Figure 3.
 a) Actively-targeted PET/ T_1 -MR dual-modality imaging of tumors with ^{64}Cu - Mn_3O_4 -TRC105 NPs. Reproduced with permission from Ref. [29]. Copyright 2017, American Chemical Society. b) Schematic illustration of the formation of ^{64}Cu -MnO NPs. c) Passively-targeting PET/ T_1 -MR dual-modality imaging of tumors with ^{64}Cu -MnO NPs. Reproduced with permission from Ref. [28]. Copyright 2010, Royal Society of Chemistry.

Figure 4.

a) Schematic illustration of constructing PET/optical dual-modality imaging nanoprobe. b) Schematic of the hybrid (PET/optical) imaging nanoprobe, C dots, showing the core-containing Cy5 dye and surface-attached PEG chains that bear cRGDY peptide ligands (binding to human $\alpha_v\beta_3$ integrin-expressing tumors) and ^{124}I radiolabels. Reproduced with permission from Ref. [8b]. Copyright 2014, American Association for the Advancement of Science. c) NP combinations with CL allow improved *in vivo* imaging (i.e., CL, CRET, and PET imaging). Reproduced with permission from Ref. [39]. Copyright 2017, Nature Publishing Group.

Figure 5.

a) Negative-stained TEM image of dried nanonaps. Scale bar, 50 nm. b) Multimodal intestinal transverse plane in a mouse with PA signal (color) and simultaneous US (grey) acquisition following gavage of 100 ODs of nanonaps. c) Nanonap movement in the intestine. Black arrow shows inflow and white arrow shows outflow. d) Nanonap labeling using ^{64}Cu . e) Representative PET imaging of nanonaps. 100 ODs of ^{64}Cu -labelled nanonaps were gavaged, and mice were imaged at the indicated time points. Scale bars, 1 cm. f) Representative 0.8-mm-thick coronal slices through the mouse, 3 h after gavage. Reproduced with permission from Ref. [50]. Copyright 2014, Nature Publishing Group.

Figure 6.

a-c) Schematic illustration of magnetic NPs as matrices to construct PET-based tri-or-more modality imaging nanoprobe. Lower panel in a-c): TEM images of $\text{Bi}_2\text{Se}_3/\text{FeSe}_2$, IONPs@UCNPs ($\text{NaYF}_4:\text{Yb/Tm}$), and IONPs-Au nanostructures, respectively. d) PET/MR/CT/PA tetra-modal imaging with ^{64}Cu - $\text{Bi}_2\text{Se}_3/\text{FeSe}_2$ -PEG. a) and d) Reproduced with permission from Ref. ^[9b]. Copyright 2016, Wiley-VCH. b) Fe_3O_4 @UCNPs, Reproduced with permission from Ref. ^[58]. Copyright 2016, American Chemical Society. c) IONPs-Au, Reproduced with permission from Ref. ^[59]. Copyright 2013, Elsevier Ltd.

Figure 7.

a) Schematic diagram of the PoP-UCNP structure and ^{64}Cu radiolabeling. b) TEM image of Pop-UCNP. High-magnification inset demonstrates the crystalline structure and UCNP core/shell geometry. c) Hexamodal *in vivo* lymphatic imaging using PoP-UCNPs in mice via fluorescence imaging (FL), upconversion luminescence (UCL) imaging, PET, PET/CT, Cerenkov luminescence (CL) imaging, and photoacoustic (PA) imaging. Reproduced with permission from Ref. [9c]. Copyright 2015, Wiley-VCH. d) Schematic diagram of the synthesis of ^{64}Cu -MNPs for PET/MRI/PA multimodality molecular imaging of tumors. Reproduced with permission from Ref. [66]. Copyright 2014, American Chemical Society.