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Surface Modified Persistent Luminescence Probes for Biosensing and Bioimaging: A Review

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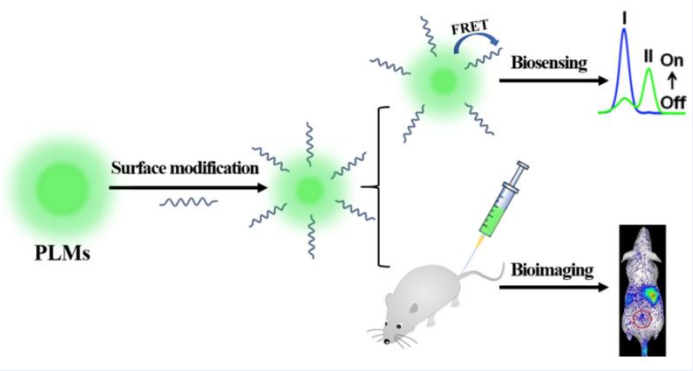
Abstract



Persistent luminescence materials (PLMs) are a class of unique luminescent materials that can remain luminescent for a few milliseconds to days without constant excitation. By virtue of the super long decay time, PLMs have been extensively explored in biosensing and bioimaging applications to elimin ate autofluorescence interference and improve signal-to-noise ratio in complex samples and tissues. However, nude PLMs often suffer from the poor stability, selectivity, and biocompatibility in biological system and *in vivo*, which greatly impedes their applications in biomedicine and bioanalysis. Remarkably, surface modification is a viable solution that endows PLMs with span-new features and can make PLMs suitable for organisms by altering PLMs' interaction with biological system. In this review, commonly used strategies for surface modification of PLMs are briefly introduced, and the applications of surface modified PLMs in biosensing and bioimaging as well as their challenges are summarized.

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1. Introduction

Persistent luminescence is that the afterglow of materials exists for a few milliseconds to several days after the excitation source being turned off.[1] In the past decades, various prominent persistent luminescence materials (PLMs) have been prepared such as $SrAl_2O_4:Eu^{2+}$, Dy^{3+}.[2] Some of them are routinely applied to many important fields including emergency signage and panel displays owing to their super long afterglow life and strong persistent luminescence.[3] As late as 2007, PLMs were reported for *in vivo* imaging by Scherman *et al.* for the first time.[4] Thereafter, researchers became aware of the enormous potential of PLMs in biosensing and bioimaging and a mass of work has been explored with respect to tumor imaging,[5] cell migration tracking,[6] biomolecule detection[7] and the like. Notably, PLMs can keep emitting light without continuous *in situ* excitation by which the autofluorescence interference elicited by biological system itself can be effectively eliminated and accordingly provide superior signal-to-noise ratio (SNR).[8] Hence, PLMs' remarkable performance makes long-term bioimaging possible and greatly improves the sensitivity of biosensing and bioimaging comparing with conventional luminescence materials. Considered to be a class of excellent optical probes, PLMs have therefore gained extensive attention and opened up new directions in biomedicine and bioanalysis fields.

Featuring with many outstanding optical properties, however, PLMs are still confronting some intractable challenges in biological applications. In biological system, the dispersibility and stability of PLMs can be affected by many factors (*e.g.*, pH, ion strength, polysaccharides and proteins), leading to poor monodispersity of PLMs in biological systems and reducing the stability of bioimaging.[9] In addition, PLMs show inferior targeting ability or insufficient specific recognition ability in complex biological systems, which vastly lowers the selectivity of bioimaging.[10] Another problem is that PLMs can be captured by spleen, liver and lung, giving rise to toxicity and biological incompatibility in living organisms when applied to bioimaging.[11-12] Thus, further improvements are urgently needed to enhance the performance of PLMs in biological systems. Surface modification is an essential approach to change the interaction between PLMs and biological substance, holding great promise for improving PLMs' performance in biological applications. By surface modification, electrostatic repulsions or steric hindrance can be introduced on the surface of PLMs to prevent their aggregation in solution.[9] The selectivity can also be brought when PLMs are modified with some molecules that have target identification ability, such as nucleic acid.[13] Furthermore, PLMs can exhibit better biocompatibility and lower toxicity with the modification of some less noxious chemicals such as poly(ethylene glycol) (PEG).[14] By means of surface modification, the interaction between PLMs and biological system can be easily tuned, thus endowing PLMs with immensely improved ability in bioimaging and biosensing. The advantages of surface modification build a bridge between the engineering of PLMs and their biosensing and bioimaging applications in complex biological systems, whereby we can extent their applications to biomedicine and other fields.

With a deeper exploration of PLMs in bioimaging and biosensing, plenty of groundbreaking work has been reported and some insightful reviews have also been published. Heretofore, Zhang *et al.* summarized the advances of PLMs in synthesis methods, bioapplications, biosafety and biomembrane modification.[8] Yuan *et al.* recently highlighted the progress in designing near-infrared (NIR) PLMs-based probes and their applications in time-resolved bioimaging and biosensing.[15] Richard *et al.* presented a summary about the multifarious applications of persistent luminescence nanoparticles (PLNPs) and discussed the future biomedical applications.[16] However, to the best of our knowledge, surface-modified PLMs and their indispensable roles in biological applications are seldom reviewed. On this account, in this work we summarized the common surface modification methods and the advances of surface-modified PLMs in biosensing and bioimaging fields, and challenges and prospects of this field are also discussed.

2. Surface Modification of PLMs

Surface modification, that is the functional groups modified on surface, is widely used to improve the stability, selectivity, biocompatibility and other performance of PLMs, which makes them more suitable for bioimaging and biosensing applications. For example, surface modification with cetuximab (CTX), an antibody, imparts to $LiGa_5O_8$:Cr the ability to specifically accumulate in lung tumor.[17] And PEG is often used to help PLMs avoid capture or degradation by reticuloendothelial system.[18] As probes for biosensing, PLMs can keep emitting light without continuous *in situ* excitation and accordingly provide superior SNR. Therefore, they need to be stable, selective and biocompatible enough to ensure that their unique luminescence property can be fully played in biological samples. Moreover, luminescence imaging features modest spatial resolution and thus there is an urgent need to improve the imaging resolution of PLMs by enhancing the stability and selectivity. Facing these challenges in biosensing and bioimaging, PLMs need more stringent and well-designed surface modification to improve the detection accuracy and imaging resolution. In a bid to give readers an overview of the superior performance of surface modified-PLMs in biosensing and bioimaging, many commonly used surface modification methods for improving the stability, selectivity, biocompatibility and other performance of PLMs-based imaging will be discussed in this section. To better demonstrate the approaches for surface modification of PLMs, the summary of various modifiers used for improving the performance of PLMs in different aspects is shown in Table 1.

2.1. Surface modification for improved stability

The stability of PLMs is essential for proper distribution of PLMs in living organisms. Some small molecules can offer better chemical stability and imaging capabilities to PLMs. For instance, the main drawback of $SrAl_2O_4:Eu^{2+}$, Dy^{3+} (SAO) is the bad water-resistance and stability, denoting that SAO is easily hydrolyzed in water.[19] To overcome this problem, pyrophosphoric acid (PPA) was used for modification of SAO to give a negatively charged surface by Zhang *et al.* to avoid its hydrolysis.[20] After being grafted by PEG, the PPA-modified SAO can be dispersed stably in

Table 1 Summary of various modifiers used for improving the performance of PLMs

PLM	Modifier	Enhanced performance	Reference
$SrAl_2O_4:Eu^{2+}$, Dy^{3+}	PPA	Stability	[19]
$ZnGa_{1.995}O_4:Cr_{0.005}$	Hydroxyl groups	Stability	[21]
Zn_2GeO_4:Mn	Complementary sequences of miRNA-21	Selectivity	[13]
$Sr_{1.6}Mg_{0.3}Zn_{1.1}Si_2O_7:Eu^{2+}$, Dy^{3+}	Complementary sequences of miRNA-21	Selectivity	[27]
$ZnGa_2O_4:Cr^{3+}$	Ins binding aptamer	Selectivity	[28]
$Ca_{1.86}Mg_{0.14}ZnSi_2O_7:Eu^{2+}$, Dy^{3+}	PSA antibody	Selectivity	[29]
$Cr^{3+}_{0.004}:ZnGa_2O_4$	KGPNQC	Selectivity	[32]
$ZnGa_2O_4:Cr^{3+}$, Sn^{4+}	Hyaluronic acid	Selectivity	[34]
Zn_2SnO_4:2%Cr^{3+}, 3%Eu^{3+}	Folic acid	Selectivity	[35]
$Ca_{0.2}Zn_{0.9}Mg_{0.9}Si_2O_6$: Eu^{2+}, Dy^{3+}	Rak-2	Selectivity	[37]
$LiGa_5O_8:Cr^{3+}$	PEG	Biocompatibility	[14]
$LiGa_5O_8:Cr^{3+}$	Polyethylenimine	Biocompatibility	[43]
$Zn_{1.25}Ga_{1.5}Ge_{0.25}O_4:Cr^{3+}$, Yb^{3+}, Er^{3+}	Red blood cell membrane	Biocompatibility	[45]
$Zn_{1.1}Ga_{1.8}Ge_{0.1}O_4$:0.5%$Cr^{3+}$, 0.5%$Eu^{3+}$	Mesoporous silicon	Therapy tracing	[47]
$Zn_{2.94}Ga_{1.96}Ge_2O_{10}:Cr^{3+}$, Pr^{3+}	Gadolinium complexes	Multimodal bioimaging	[49]
$Zn_{2.94}Ga_{1.96}Ge_2O_{10}:Cr^{3+}$, Pr^{3+}	TaO_x	Multimodal bioimaging	[50]

sodium chloride solution. Then, the SAO nanoparticles were excited by ultraviolet lamp for 10 min and intravenously injected into the mouse. The afterglow signals can last for more than 30 min. The imaging signals can be recovered by re-excited for another 30 min (Figure 1A).

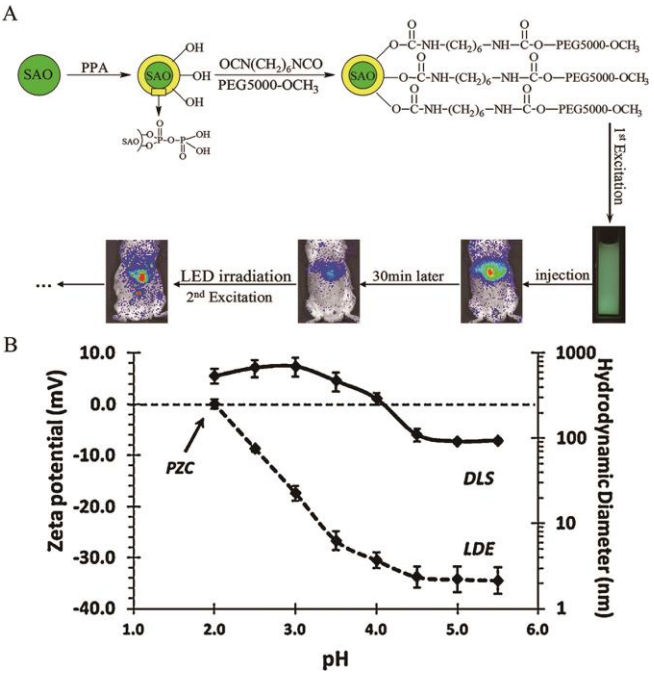

Figure 1 (A) Illustration of modification and afterglow bioimaging of SAO nanoparticles. Reprinted with permission.[20] (B) Stability characterization of ZGO-OH in solution. Reprinted with permission.[21]

Suspension stability of PLMs can be affected by many factors in dispersion media and even result in agglomeration/aggregation. Introducing electrostatic repulsions to PLMs is an effective way to prevent their aggregation in aqueous solution. In this case, Varenne *et al.* synthesized $ZnGa_{1.995}O_4:Cr_{0.005}$ (ZGO) PLNPs and the surface of ZGO was functionalized by hydroxyl groups to obtain negatively charged ZGO-OH nanoparticles.[21] By combining the characterization methods of laser doppler electrophoresis, dynamic light scattering, and capillary zone electrophoresis, colloidal stability of ZGO-OH through time was determined systematically when dispersed in multifarious buffers. Results showed that ZGO exhibited excellent colloidal stability after being modified by hydroxyl groups at surface in various physiological buffers with changed pH and ionic strength (Figure 1B). It is worth noting that hydrothermal synthesis is a very common method used for the synthesis of PLMs, by which plenty of hydroxyl groups can be introduced on the surface of PLMs. Compared to other kind of nanomaterials, modifiers that can conjugate with hydroxyl groups are particularly easy and suitable to be further functionalized on the surface of PLMs.

2.2. Surface modification for enhanced selectivity

There are many specific recognitions in biomacromolecules such as base pairing,[22] enzyme and substrate,[23] antigen and antibody,[24] aptamer and its target[25] and so on. When these specific interactions are introduced into PLMs *via* biomacromolecules, PLMs' selectivity toward target will be greatly enhanced.

For example, Yuan *et al.* constructed a time-gated luminescent biochip based on Zn_2GeO_4:Mn (ZGO:Mn) long-lifetime luminescence nanoparticles for detection of miRNA-21, a bladder cancer-related biomarker, in urine samples.[13] The surface of ZGO:Mn was modified with DNAs that are completely paired with miRNA-21. Black-hole-quencher-labeled DNAs (BHQDNAs) that are partially complementary to miRNA-21 were employed as the quencher of ZGO:Mn due to the fluorescence resonance energy transfer (FRET) between BHQDNAs and ZGO:Mn. When miRNA-21 exists, the FRET system was destroyed following the dissociated BHQDNAs, and the long-lifetime luminescence was restored (Figure 2A). Through base pairing, the DNAs-functionalized PLMs achieved specific cancer biomarker detection in complex samples and the detection limit was as low as 26.3 fM. Ju *et al.* also reported the biosensing of miRNA-21 based on time-resolved FRET (TR-FRET).[26] DNA1 was modified on the surface of Eu^{2+} and Dy^{3+} co-doped $Sr_{1.6}Mg_{0.3}Zn_{1.1}Si_2O_7$ PLNPs. Partial hybridization can occur between Fluorescein isothiocyanate (FITC)-labeled DNA2, miRNA-21 and DNA1, and the TR-FRET can happen from the nanoparticles to FITC to quench the luminescence. With the increase of the concentration of miRNA-21, TR-FRET signals of FITC increased so that the detection of miRNA-21 was realized (Figure 2B). Among the well-studied biomacromolecules, aptamers (RNA or

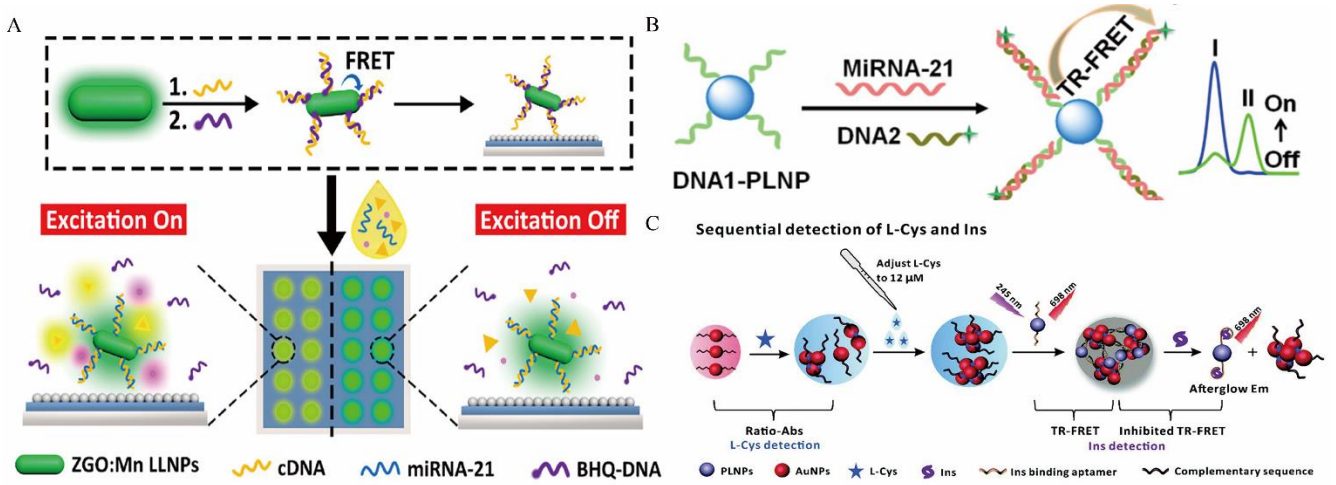

Figure 2 (A) Schematic illustration of single-stranded DNAs-modified ZGO:Mn LLNPs for time-gated detection of miRNA-21 in urine samples. Reprinted with permission.[13] (B) Schematic illustration of TR-FRET detection strategy for miRNA-21 based on DNA-modified PLNPs. Reprinted with permission.[26] (C) Schematic of TR-FRET nanoplatform based on aptamer functionalized PLNPs for detection of *L*-Cys and Ins. Reprinted with permission.[28]

DNA oligonucleotides gained from SELEX) have drawn much attentions due to their high affinity and specificity to their targets,[27] and have been widely investigated in PLMs modification. Yan *et al.* developed an aptamer-functionalized TR-FRET nanoprobe for monitoring the concentration of *L*-cysteine (*L*-Cys) and insulin (Ins) in human serum based on $ZnGa_2O_4:Cr^{3+}$ PLNPs and Au nanoparticles (Au NPs) (Figure 2C).[28] Firstly, the PLNPs were modified with Ins binding aptamer (IBA) and AuNP was functionalized with complementary sequence (CS) to give PLNP-IBA and AuNP-CS respectively. AuNP-CS aggregated due to the existence of *L*-Cys and induced the bathochromic shift of the absorb light of AuNP-CS, thus the detection of *L*-Cys was achieved. Then the persistent luminescence of PLNP-IBA was quenched by aggregated AuNP-CS to form a TR-FRET system. But the persistent luminescence was easily recovered in the presence of Ins which can strongly bind with the PLNP-IBA. This strategy provided a dual-signaling platform for biosensing in complex biological samples.

Immunoassay is a powerful tool for biosensing because of the high specificity and reactivity of antibody.[29] For example, Yan *et al.* combined the FRET assay with ratiometric luminescent detection based on the antibody-modified PLNPs to improve the detection sensitivity and accuracy.[30] Specifically, prostate-specific antigen (PSA) is a susceptive biomarker of prostate carcinoma. They constructed a FRET system by employing the PSA antibody (PS6)-modified $Ca_{1.86}Mg_{0.14}ZnSi_2O_7:Eu^{2+}$, Dy^{3+} PLNPs as the energy donor and another mouse monoclonal PSA antibody (8A6) bioconjugated Rhodamine B (RhB) (RhB-8A6) as the energy acceptor (Figure 3A). With the increasing level of PSA, the FRET was happened and the rate of the luminescent strength of RhB to PLNPs increased. The specific antigen-antibody recognition makes PLNPs-based FRET effect more sensitive, reliable and applicable to detect other biomarkers. Apart from antibody, many other peptides have unique properties, and endow PLMs with some interesting functions by surface modification. For instance, to realize the biosensing and bioimaging of fibroblast activation protein-alpha (FAPα), a biomarker related to many cancers such as breast cancer, bladder cancer and lung cancer,[31] Wang *et al.* constructed an afterglow resonance energy transfer (ARET) system that Cy5.5-KGPNQC-SH was modified on the surface of Au-coated $Cr^{3+}{}_{0.004}:ZnGa_2O_4$ to quench its luminescence (Figure 3B).[32] KGPNQC is a peptide that can be cleaved by FAPα. Therefore, in the presence of FAPα, the ARET process was inhibited because of the breakage of KGPNQC. Furthermore, this probe can monitor the FAPα of FAPα-positive cells, which also demonstrated the admirable selectivity of this nanoprobe for biosensing. The peptide modified on the surface provided high sensitivity and combined with the anti-interference capability of PLMs, making the probe an ideal candidate for bioanalytical applications in complex samples.

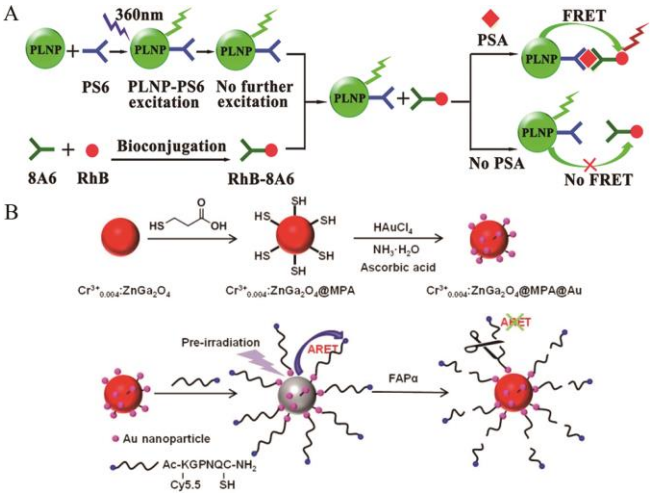

Figure 3 (A) Schematic illustration of antibody functionalized PLNPs for FRET immunoassay of PSA. Reprinted with permission.[30] (B) Schematic illustration for surface modification of $Cr^{3+}{}_{0.004}:ZnGa_2O_4$ as the ARET system for FAPα detection. Reprinted with permission.[32]

In addition, the enhanced selectivity of imaging can be realized through receptor-mediated specific recognition by surface modification. For example, cluster determinant 44 (CD44) is a kind of receptor that is overexpressed in cancer cells and can interact with polymer hyaluronic acid (HA). Therefore, HA has been investigated intensively in the field of tumor-targeting bioimaging.[33] In 2019, Fu *et al.* constructed a tumor-targeting and drug delivery nanoplatform based on HA and mesoporous silicon.[34] $ZnGa_2O_4:Cr^{3+}$, Sn^{4+} (ZGCS) coated with drug-loaded mesoporous silicon was employed to realize afterglow imaging of cancer cells and drug delivery after being modified with HA (Figure 4A). Excellent tumor-targeting ability gained from HA modification makes PLMs-HA a promising platform for imaging-guided cancer therapy.

Some small molecules are also promising candidates for tumor targeting. Folate receptors (FRs) stay at a low level in normal tissues. However, FRs are overexpressed in malignant tumors such

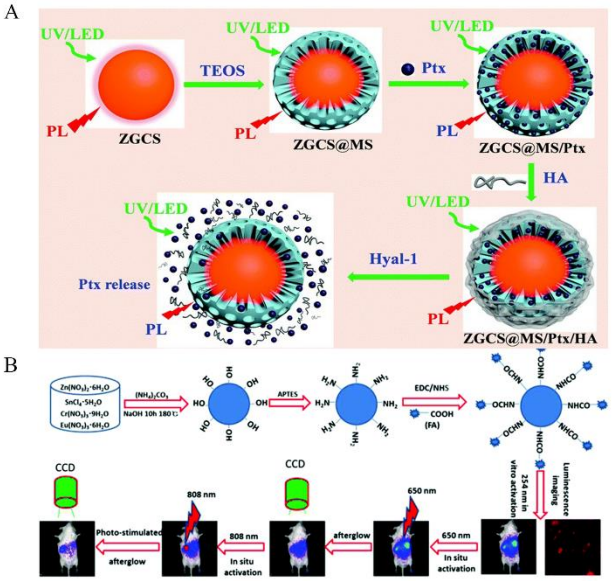

Figure 4 (A) Schematic of HA-modified ZGCS for afterglow imaging of cancer cells and drug delivery. Reprinted with permission.[34] (B) Schematic illustration of the FA modified Zn_2SnO_4:2%Cr^{3+}, 3%Eu^{3+} for repeated *in vivo* deep tissue bioimaging. Reprinted with permission.[35]

as breast, lung, kidney cancers. Therefore, Folic acid (FA) is another frequently used small molecule for surface modification of PLMs.[36] In 2017, Zhang *et al.* constructed a NIR-emitting nanoprobe of Zn_2SnO_4:2%Cr^{3+}, 3%Eu^{3+} with afterglow emission at 800 nm.[35] FA was modified on their surface for tumor targeting and thus the accurate cancer cells imaging was achieved successfully with 3 cm tissue penetration (Figure 4B). In 2010, Khandadash *et al.* found a compound Rak-2 can strongly bind to PC-3 cells through a molecule screening system.[37] Later researchers reported a further work that they modified Eu^{2+}, Dy^{3+}-doped $Ca_{0.2}Zn_{0.9}Mg_{0.9}Si_2O_6$ persistent phosphor with Rak-2 and the modified persistent phosphor was proved to have high affinity toward PC-3 cells *in vitro*.[38] Besides FA and Rak-2, biotin is another important small molecule for surface modification of PLMs because biotin-avidin system is highly specific and widely used in bioanalysis.[39]

2.3. Surface modification for better biocompatibility

With the development of the biological applications of PLMs, a lot of polymers have been used for their surface modification. The function of polymers mainly focuses on improving the biocompatibility and increasing circulation time of PLMs in body.[40]

Among the explored polymers, PEG is one of the most common candidates by the virtue of its biodegradability, nontoxic nature, and absence of antigenic and immunogenic effects.[41] As an example, PEG was modified on the surface of $LiGa_5O_8$:Cr^{3+} nanoparticles (LGNPs) for *in vivo* bioimaging.[14] LGNPs were prepared through the sol–gel method, and then the PEGylation was performed on the surface of LGNPs (Figure 5A). Cr^{3+}, a prominent emission center in PLMs, is highly toxic, but PEGylated LGNPs showed excellent biocompatibility and less poisonousness

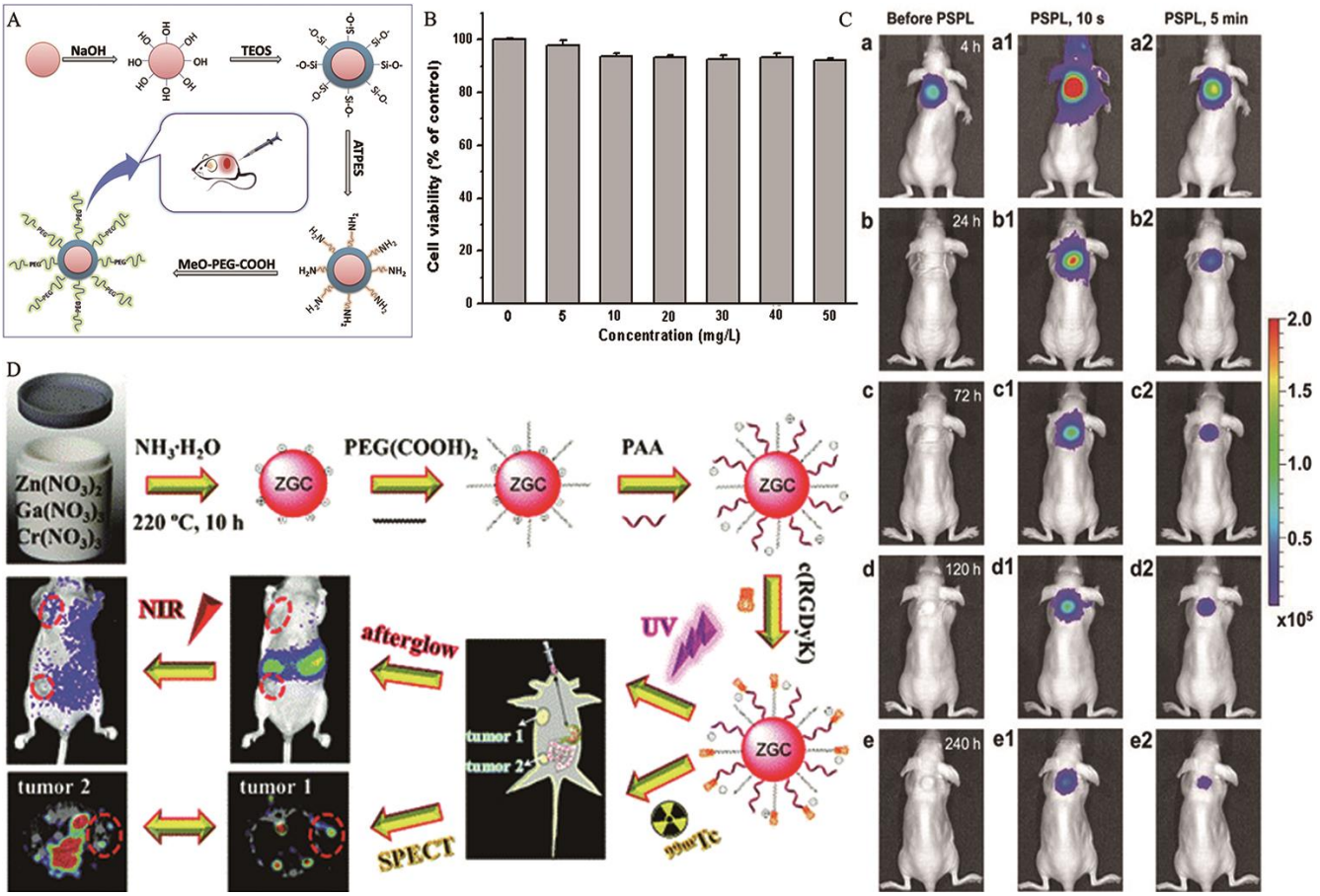

Figure 5 (A) Illustration of the PEGylation of LGNPs. (B) Toxicity test of PEG-modified LGNPs on human umbilical vein endothelial cells. Reprinted with permission.[14] (C) *In vivo* tracking of PEI-$LiGa_5O_8$:Cr^{3+} PLNPs labeled 4T1 cells for 10 d. Reprinted with permission.[43] (D) Schematic illustration for the preparation, surface modification of $ZnGa_2O_4$:Cr^{3+} nanocrystals by PEG and PAA, and *in vivo* bioimaging. Reprinted with permission.[44]

comparing with nude LGNPs (Figure 5B). Also, the *in vivo* distribution of the LGNPs can be detected longer than 1 h, which indicated the bioimaging potential of PEG-modified PLMs. Polyethylenimine (PEI) is a polycation molecule and a common additive as well, because PEI can favor the internalization of nanoparticles into cells.[42] Pan *et al.* used PEI for the surface modification of LGNPs, and the 4T1 cells were labeled with PEI-functionalized LGNPs successfully.[43] The labeled cells can be monitored for more than 10 d with repeated rejuvenation after injection into a nude mouse (Figure 5C), demonstrating that the internalized nanoparticles are dominant *in vivo*. In addition, two polymers can be used to modify PLMs simultaneously to provide multifunctional surface. For example, Li *et al.* prepared the Cr^{3+}-doped $ZnGa_2O_4$ PLMs through a one-step method.[44] Then their surface was modified with PEG and poly(acrylic acid) (PAA), a linker between nanoparticles and other molecules, to provide good biocompatibility and functional groups for further conjugating with c(RGDyK). And after being labeled with radioactive nuclide ^{99m}Tc, the nanoprobe can achieve *in vivo* afterglow and single-photon emission computed tomography/computed tomography imaging of rats (Figure 5D).

Biomembrane modification is another important strategy to improve PLMs' biocompatibility. For instance, to further improve the ability of persistent luminescent nanocarriers to penetrate the biological barriers, Wang *et al.* developed biomimetic strategy to fabricate optical nano-carriers for *in vivo* afterglow imaging and drug delivery.[45] Red blood cell (RBC) membrane was used to functionalize the mesoporous silica coated $Zn_{1.25}Ga_{1.5}Ge_{0.25}O_4:Cr^{3+}$, Yb^{3+}, Er^{3+} and thus the long-circulating of PLNPs and improved biocompatibility was realized to give better therapeutic effect and realize the long-term bioimaging.

2.4. Surface modification for multifunctional platform

In order to meet the diversified needs of PLMs-based imaging platform, some surface modification methods were developed to generate multifunctional PLMs. As an example, mesoporous silicon is often used as the modifier for drug delivery by the virtue of diverse micropore structure and large surface area.[46] Yan *et al.* constructed a drug loaded PLMs-based nanoprobe for bioimaging and chemotherapy of tumor.[47] Mesoporous silicon was coated on $Zn_{1.1}Ga_{1.8}Ge_{0.1}O_4$:0.5%$Cr^{3+}$, 0.5%$Eu^{3+}$ PLNPs. Doxorubicin was then loaded in the mesoporous channels to kill cancer cells, and the tumor imaging without autofluorescence interference was realized simultaneously (Figure 6A).

Also, metal complexes play important roles in multimodal bioimaging, therefore improving the spatial resolution of bioimaging.[48] Yan *et al.* reported some pioneering work in multimodality imaging. For instance, the surface of $Zn_{2.94}Ga_{1.96}Ge_2O_{10}:Cr^{3+}$, Pr^{3+} was modified with gadolinium complexes for magnetic resonance (MR) and NIR luminescence imaging.[49] The gadolinium complexes functionalized PLNPs exhibited high longitudinal relaxivity and long-lasting persistent luminescence. This imaging method not only provides high sensitivity and SNR, but also good spatial resolution (Figure 6B). In 2015, their research group reported another work in multimodal bioimaging field.[50] A TaO_x layer was coated on the surface of $Zn_{2.94}Ga_{1.96}Ge_2O_{10}:Cr^{3+}$, Pr^{3+} PLNPs to form the core-shell structure and the TaO_x acted as the contrast agent for X-ray computed tomography (CT) imaging. With further functionalization, the core-shell structure PLNPs can realize tumor NIR persistent luminescence and CT imaging. In short, many new functions mentioned above are imparted to PLMs by surface modification, which make them more suitable for biological applications.

3. Biosensing Based on Modified PLMs

The most important character of PLMs is that they can remain luminescence after switching off the excitation source. Therefore, the background fluorescence interference of samples can be effectively eliminated and a superior SNR can be provided in PLMs-based biosensing. With the surface modification, PLMs become more stable, biocompatible and show better selectivity in biological applications. These merits make PLMs ideal candidates for complicated biosensing of tumor biomarkers, bioactive molecules, physiological parameters, *etc.*

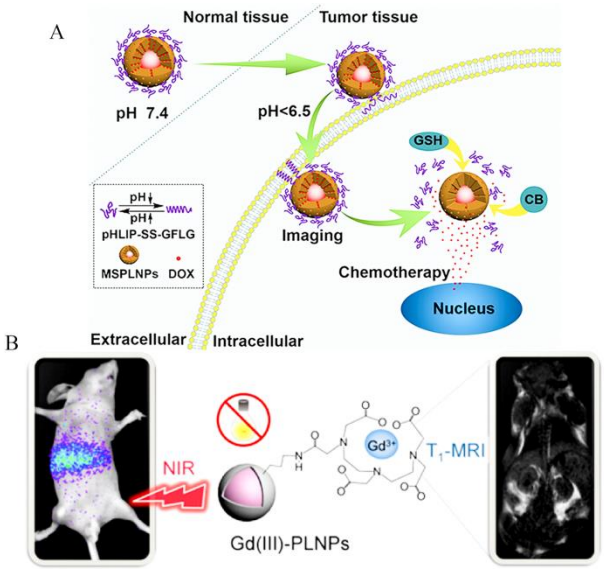

Figure 6 (A) Schematic illustration of mesoporous silicon-modified PLNPs for imaging and chemotherapy of tumor. Reprinted with permission.[47] (B) DTPA-Gd modified PLNPs for NIR luminescence and MR imaging. Reprinted with permission.[49]

3.1. Tumor biomarkers

Better therapeutic effect of cancers can be obtained with accurate early diagnosis. The level of many molecules, *i.e.* tumor biomarkers, changes at the early stage of diseases.[51] Therefore, quantitative detection and real-time sensing of biomarkers are of great importance in medical treatment. Many methods based on PLMs have been developed for biosensing of biomarker in early diagnosis.

Carcinoembryonic antigen (CEA) is considered to be related to many cancers such as prostatic cancer.[52] PSA is also a biomarker associated with prostate cancer as introduced in a previous section. Based on these principles, Zhao *et al.* developed an autofluorescence-free dual-channel fluorescence biosensor for detecting CEA and PSA simultaneously.[53] They synthesized NIR-emitted Cr^{3+} doped $ZnGa_2O_4$ (ZGC) and green-emitted Mn^{2+} doped Zn_2GeO_4 (ZGO:Mn) persistent luminescence nanorods (PLNRs). And they were modified with CEA binding aptamer and PSA binding aptamer on the surface respectively. Both of these two PLNRs were quenched by polydopamine nanoparticles (PDANSs) at first to fabricate the FRET system. The luminescence can be restored in the presence of CEA and PSA, and the detection limits were 8.9 $fg{\cdot}mL^{-1}$ PSA and 72 $fg{\cdot}mL^{-1}$ CEA (Figure 7A). This dual-channel nanoprobe provided a promising strategy for high throughput cancer early diagnostics. The serum levels of α-fetoprotein (AFP) often increase during the fast growth of liver tumor cells.[54] Accordingly, the biosensing of AFP is helpful for diagnosis of liver cancer. In 2011, Yan *et al.* prepared $Ca_{1.86}Mg_{0.14}ZnSi_2O_7$: Eu^{2+}, Dy^{3+} PLNPs and the surface was functionalized with PEI.[55] AFP-antibody-coated Au nanoparticles (Ab-AuNPs) were further conjugated to quench the persistent luminescence through FRET. The FRET process can be inhibited in the presence of AFP for the strong binding with the antibody, thus realizing sensitive and accurate detection of AFP.

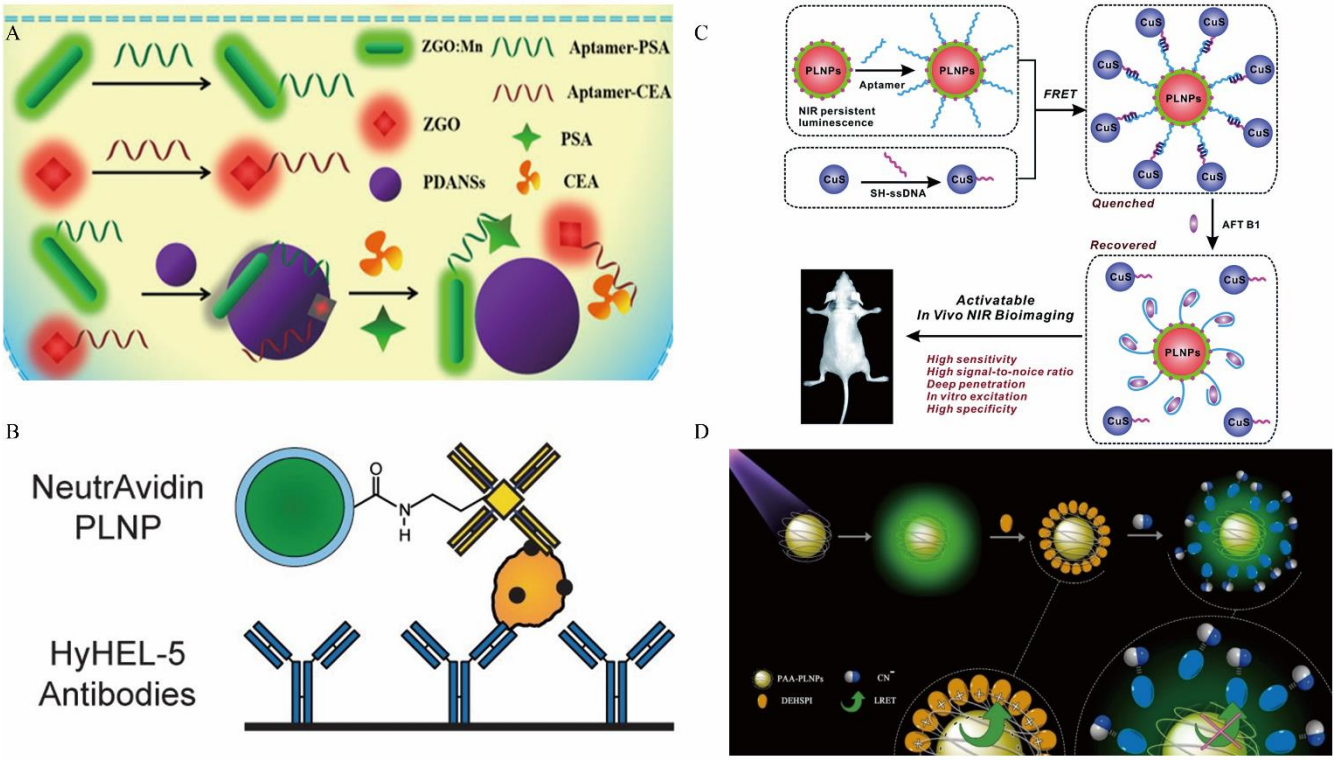

Figure 7 (A) Schematic illustration of dual-channel autofluorescence-free biosensor for PSA and CEA. Reprinted with permission.[53] (B) Schematic illustration of NeutrAvidin functionalized $SrAl_2O_4:Eu^{2+},Dy^{3+}$ PLNPs for lateral flow assay of lysozyme. Reprinted with permission.[39] (C) Design and fabrication of aptamer-modified PLNPs-involved FRET system for *in vivo* determination of aflatoxin. Reprinted with permission.[56] (D) Schematic illustration of PAA-modified PLNPs-based nanoprobe and its response to CN^-. Reprinted with permission.[57]

3.2. Bioactive molecules

Bioactive molecules have many functions such as signal transduction and substance transportation.[58] Monitoring the content of these bioactive molecules is pivotal in human health and disease diagnosis. Notably, lysozyme can hydrolyze the mucopolysaccharides of bacteria and its overexpression is related to various diseases, such as AIDS,[59] sarcoidosis[60] and so on. Willson *et al.* employed NeutrAvidin functionalized $SrAl_2O_4:Eu^{2+}$, Dy^{3+} PLNPs as the reporter of lateral flow assays to detect biotinylated lysozyme (Figure 7B).[39] Firstly, the lysozyme was captured by an anti-lysozyme HyHEL-5 antibody on the test strip and then the biotinylated lysozyme was labeled by NeutrAvidin PLNPs through Biotin-Avidin binding. This strategy combined the point-of-care assay with the advantage of autofluorescence-free biosensing, thus providing high sensitivity and enough conveniences.

Like health care, food safety is of great concern in our daily life. Aflatoxins (AFT) can be generated by some fungi, which are extremely carcinogenic toxins in spoiled food.[61] Wang *et al.* fabricated a persistent luminescence nanoprobe for determination of AFT B1 *via* the FRET strategy both *in vitro* and *in vivo*.[56] Aptamer-modified $Zn_{1.2}5Ga_{1.5}Ge_{0.25}O_4$:0.5%$Cr^{3+}$, 2.5%$Yb^{3+}$, 0.25%$Er^{3+}$ PLNPs was used as emission center and single-strand DNA modified CuS was utilized as the quencher. DNA hybridization between aptamer and single-strand DNA was broken because of the higher attraction of aptamer to AFT B1, which led to the recovery of luminescence (Figure 7C). This work achieved specific detection of AFT B1 without autofluorescence interference and provided an insight towards PLMs for the food safety applications.

3.3. Other physiological parameters

In addition to tumor biomarkers and bioactive molecules, some other important biosensing applications based on surface-modified PLMs were also explored. Cyanide (CN^-) is exceedingly toxic to human because the cytochrome oxidase can be inhibited by CN^-. In this case, Lv *et al*. developed a luminescence resonance energy transfer (LRET) effect-based nanoprobe to detect CN^-.[57] The probe consists of two main parts, of which PAA-modified $ZnGa_2O_4:Mn^{2+}$ PLNPs were employed as the energy donor and 4-[4-(*N*,*N*-diethylamino)-2-hydroxy-styryl]-*N*-methylpyridinium iodide (DEHSPI) was employed as the acceptor and recognition unit. CN^- can result in the luminescence recovery of PLNPs (Figure 7D). Furthermore, CN^- in living cells can also be determined with excellent analytical performance and low cytotoxicity. It's also worth noting that body temperature is one of the most important physiological parameters. Monitoring slight changes in temperature is helpful to disease diagnosis. To fulfill accurate temperature detection, Liu *et al.* studied the influence of Ge^{4+} concentrations ($0.45 \leqslant x \leqslant 0.90$) on the temperature sensing capability of $Zn_2Ga_{3.98-4x/3}Ge_xO_8:Cr_{0.02}$ (ZGGO:Cr) PLNPs.[62] They found when x = 0.90, the PLNPs can be used as a nanothermometer due to the change of afterglow intensity with temperature and the detection range was located in physiological temperature range, which proved its potential to monitor the slight alterations in temperature during diagnosis and treatment.

4. Bioimaging Based on Modified PLMs

Fluorescent bioimaging is a noninvasive method that allows monitoring various biological processes in their native contexts and has been proved to be an indispensable tool in modern biological study.[63] Many fluorescent probes have been developed including organic dyes, fluorescent proteins, and metal complexes. However, the autofluorescence interference from tissues or substances can be elicited during the excitation process of these flu-

orescent probes. Inversely, PLMs are ideal alternatives for bioimaging because of their super long afterglow time and thus the tissue autofluorescence can be effectively eliminated to give a high SNR. Furthermore, with the large specific surface area, PLMs surface can be easily modified with polymers, small molecules, biomacromolecules and so on, after which PLMs are more suitable for extensive bioimaging applications. In this section, bioimaging applications of PLMs at different scales will be introduced in details

4.1. Molecular imaging

Accurate molecular imaging is of significant importance to give the real time picture of pathologies and helps to achieve early diagnosis of diseases at molecular level.[64] Up to now, a lot of work utilizing PLMs to realize highly sensitive and selective long-time molecular imaging in living systems has been published.

Biological thiols are a group of small molecules that contain mercapto groups. Among them, GSH, which has been mentioned in previous section, is the richest intracellular thiol that plays a vital role in pathological conditions.[65] Moreover, GSH content was reported to be highly related to cancers. To give a real-time visualization of GSH in tumor, Lv *et al.* developed a near-infrared persistent luminescence (NIR PersL) nanoplatform for *in vitro* and *in vivo* imaging of GSH.[66] $ZnGa_2O_4:Cr^{3+}$ PLNPs were modified with (Di-(2-Picoly) Amine) (DPA) for further conjugation of Cu^{2+} which can quench the NIR PersL. GSH can react with Cu^{2+} and lead to the removal of Cu^{2+}, so that the NIR PersL was recovered. Compared to normal cells, the NIR PersL was greatly restored in cancer cells, implying the higher levels of GSH (Figure 8A). The similar result was obtained in tumor imaging (Figure 8B), which indicated PLMs' potential for molecular imaging in complex systems.

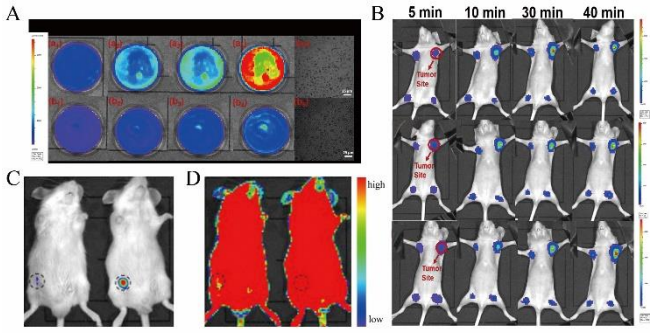

Figure 8 (A) Cell and (B) tumor persistent luminescence images of GSH. Reprinted with permission.[66] (C) Afterglow image of mice injected with saline and the nanoprobe (left) and mice injected with vitamin C and the nanoprobe (right) without excitation. (D) Photoluminescence image of the same mice in (C) using 420 nm light stimulation. Reprinted with permission.[67]

Unlike biological thiols, vitamins are essential micronutrients to many physiological and biochemical processes. The reduction of vitamins is associated with many chronic disease.[68] Tang *et al.* synthesized CoOOH nanoflakes modified $Sr_2MgSi_2O_7$:1%Eu, 2%Dy PLNPs to construct the FRET system for imaging of vitamin C in cells and *in vivo*.[67] Because of its reducibility, CoOOH can be reduced to cobalt divalent ion whereby the FRET process from PLNPs to CoOOH was stopped and afterglow was regained. After ceasing the excitation, the luminescence of PLNPs still lasts a few hours so that the background fluorescence produced *in situ* can be eliminated. Through the PLMs nanoprobe based on FRET, imaging of vitamin C in living cells and *in vivo* (Figure 8C and Figure 8D) was realized with high sensitivity.

4.2. Cellular imaging and dynamics tracking

Cell migration happens in many biological and pathological processes such as cancer metastasis, immune response and cell therapy for cancer.[69] Imaging and tracking of cell migration hold great promise to monitor these biological processes, which might be crucial to the treatment of some diseases. To give a visualization of cell migration process, many studies have been conducted by utilizing NIR PLMs as the probe to achieve both deep penetration and high sensitivity.

Metastasis leads to about 90% of tumor involved death, yet the mechanism is still unknown.[70] Recently, Yang *et al.* prepared a NIR PLNPs probe for imaging of the metastasis process.[71] $Zn_{1.1}Ga_{1.8}Ge_{0.1}O_4:Eu_{0.009}$, $Cr_{0.09}$ PLNPs were modified with 4-carboxyphenyl boronic acid (CPBA) which allowed the receptor-mediated endocytosis for breast cancer cells labeling. After further being coated with alginate to generate persistent luminescence hydrogel (PL-gel), PLNPs-CPBA can be released sustainably and thus the increased renewable afterglow was realized. Then labeled cells were injected into mice, the migration and metastasis to lung, liver, and spleen were effectively tracked without autofluorescence interference (Figure 9A). In addition, the metastasis of breast cancer often takes place *via* the axillary lymph node. Therefore, Li *et al.* used PEG functionalized PLNPs to track the metastasis process of breast cancer cells to lymph nodes for as long as 25 d and they found the metastasis happened within 3 d.[72] Compared with other optical probes, these work provided powerful tools that can be rationally designed for long-time tracking of various cancer metastasis without autofluorescence interference.

In recent years, cell therapies have received much attention for their potential to treat many diseases such as cancers.[75] Braeckmans *et al.* reported that they used lipid-coated $LiGa_5O_8:Cr^{3+}$ PLNPs to achieve *in vivo* visualization of dendritic cells (DCs) migration which were used for immunotherapy.[73] Lipid modification greatly increased the biocompatibility and stability of PLNPs in biological media. After being injected into mice, DCs labeled with lipid-coated PLNPs can be imaged for several days and the migration process from injection sites to lymph nodes was also monitored successfully (Figure 9B). Human mesenchymal stem cells (hMSCs) have shown potential to treat pulmonary fibrosis (PF). To evaluate the homing ability of intravenously injected hMSCs to the injured lungs, Wang *et al.* used poly-*L*-lysine (PLL)-modified Cr^{3+} and Eu^{3+} co-doped $Zn_{1.1}Ga_{1.8}Ge_{0.1}O_4$ PLNPs to track the migration process of PLNPs labeled hMSCs and the imaging time can last up to 30 d with high SNR (Figure 9C).[74]

In addition to tracking the metastasis process and therapeutic cells migration, many other cell migration processes were also monitored with modified PLNPs. For instance, Richard *et al.* reported the real-time *in vivo* tracking of macrophages with PEG-modified $ZnGa_{1.995}Cr_{0.005}O_4$ PLNPs.[76] And in another work, they developed the nanohybrids that contain PLNPs and magnetic nanoparticles to realize both *in vivo* long-term imaging and magnetic vectorization of endothelial colony-forming cells (ECFC).[77] The all above mentioned work not only provided approaches to realize long-term and autofluorescence-free tracking of cells but also expanded the cell-based study and application.

4.3. Tumor imaging

Tumor imaging provides plentiful information for diagnosis and treatment of cancer.[78] PLMs were broadly investigated as the probe for tumor imaging because they can avoid the autofluorescence interference to give high sensitivity and SNR. In this case, Yuan *et al.* reported a series of Cr doped $Zn_{1+x}Ga_{2-2x}Ge_xO_4$ (ZGGO:Cr) PLNPs with tunable size and afterglow properties by altering x value.[79] ZGGO:Cr nanoparticles with x = 0.2 were

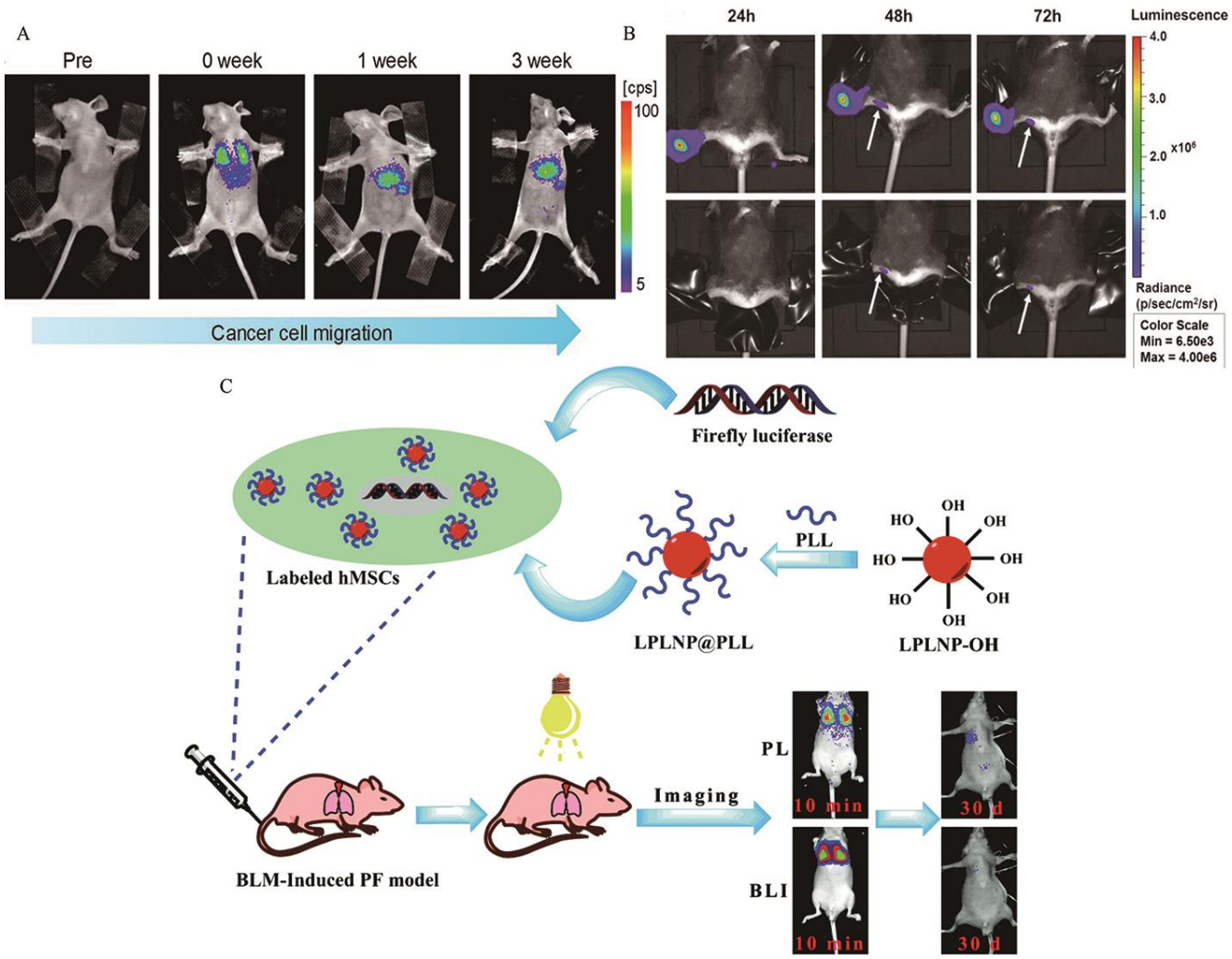

Figure 9 (A) Afterglow images of representative nude mice injected with PLNPs-CPBA-labeled cancer cells to track the cancer metastasis process. Reprinted with permission.[71] (B) Images of mice injected with PLNPs-labeled DCs acquired at several time points after injection without (top) and with (bottom) tape that masks the injections site. Reprinted with permission.[73] (C) Schematic illustration of the PLL-modified PLNPs for tracking of the transplanted hMSCs in bleomycin (BLM)-induced PF. Reprinted with permission.[74]

chosen for tumor imaging because of their super long afterglow. After being modified with 4T1 cells binding aptamer, ZGGO:Cr exhibited superb tumor-specific accumulation and the long-term autofluorescence-free tumor imaging was realized (Figure 10A). UV, visible light, or X-ray are common excitation sources for PLMs. However, excitation with these sources still faces many challenges such as short penetration depth, and insufficient charging ability. Recently, to overcome these problems, Sun *et al.* proposed a strategy that ^{18}F-fluorodeoxyglucose (^{18}F-FDG), a tumor-imaging radiopharmaceutical, was used to *in vivo* excite $ZnGa_2O_4:Cr^{3+}$ PLNPs.[80] Therefore, the renewable luminescence for tumor imaging can be obtained for several times upon injection of ^{18}F-FDG (Figure 10B).

Persistent luminescence imaging has the advantage of excellent sensitivity but its spatial resolution still needs to be improved. Combining PLNPs with other imaging contrast agent to achieve multimodal bioimaging is an effective way to solve the problem. Yan *et al.* fabricated a multifunctional nanocomposite as the nanoprobe for both NIR PL imaging and MR imaging.[81] NIR $ZnGa_2O_4:Cr^{3+}$ PLNPs were coated with HA-modified Gd_2O_3. Gd_2O_3 served as the MR contrast and the tumor-targeting capability was endowed by HA. High PL SNR and good MR spatial resolution were obtained for tumor imaging with this nanoprobe (Figure 10C). Wang *et al.* introduced Au element into $GdAlO_3:Mn^{4+}$, Ge^{4+} to promote the fluorescence efficiency through plasmon resonance and Au element also served as contrast agent of CT imaging.[83] Therefore, Au-based CT imaging and Gd-based MR imaging were combined with PL imaging and hence the trimodality bioimaging of tumor was achieved.

Imaging-guided cancer therapeutics have become one of the frontiers in current cancer therapies.[84] In recent years, developing NIR PLMs for imaging-guided cancer therapy has attracted growing attention because of their super long afterglow and deep tissue penetration. Lv *et al.* reported the synthesis of $Zn_{1.07}Ga_{2.34}Si_{0.98}O_{6.56}:Cr_{0.01}$ (Si-ZGO) as nanocarriers for NIR persistent luminescence imaging guided cancer chemotherapy.[82] Mesoporous Si-ZGO was synthesized by silica-assisted targeted etching strategy and thus doxorubic (DOX) can be loaded on the porous channels of Si-ZGO. The nanocarriers displayed good biocompatibility and colloidal stability after being modified with bovine serum albumin (BSA). After being injected into tumor bearing mice, the distribution of obtained DOX-BSA@Si-ZGO nanocarriers can be effectively monitored by *in vivo* afterglow imaging and chemotherapy of tumor was achieved successfully (Figure 10D). Moreover, PLMs can also act as the ideal *in vivo* excitation light sources for photodynamic therapy (PDT)[85] and photothermal therapy (PTT).[86]

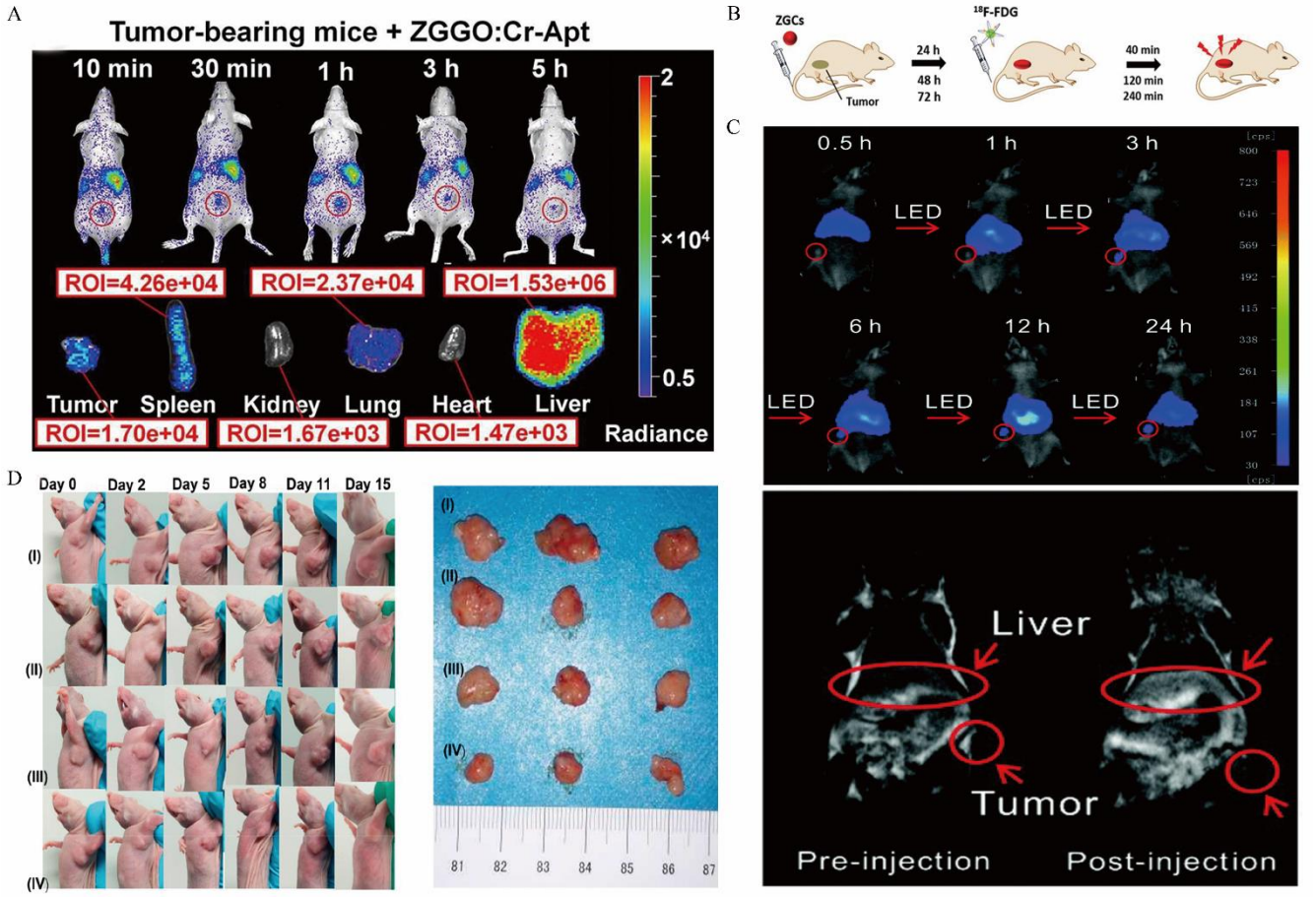

Figure 10 (A) *In vivo* and *ex vivo* photoluminescence images of tumor-bearing mice injected with aptamer-modified ZGGO:Cr PLNPs. Reprinted with permission.[79] (B) Schematic illustration of 18F-FDG excited $ZnGa_2O_4:Cr^{3+}$ for *in vivo* persistent luminescence tumor imaging. Reprinted with permission.[80] (C) *In vivo* PL images (up) and T1-weighted MR images (bottom) of tumor bearing mice after intravenous injection of HA-Gd_2O_3-PLNPs. Reprinted with permission.[81] (D) Representative images of micer treated with differtent substances (left) and representative images of tumor treated with differtent substances (right). In detail: (I) PBS only; (II) BSA@Si-ZGO, (III) free DOX, and (IV) DOX-BSA@Si-ZGO. Reprinted with permission.[82]

5. Conclusions and Perspectives

Because of the long decay time, PLMs have attracted widespread interest in recent decades. As the *in situ* constant excitation is unnecessary, PLMs can eliminate the autofluorescence interference of biological systems and a high sensitivity is obtained resultantly, which make them ideal optical probes for biological applications. However, their applications in complex biological samples are still greatly restricted by poor biocompatibility, colloidal stability, and inferior selectivity toward target. To overcome these problems of PLMs, surface modification is often conducted to make PLMs more suitable for biological applications. In this review, various widely used surface modification approaches for improved stability, enhanced selectivity, better biocompatibility, and other performance of PLMs were introduced. Also, we further discussed recent advances of modified PLMs in biosensing and bioimaging. Surface modified-PLMs offer detection superior SNR, accuracy and stability so that biosensing of tumor biomarkers, bioactive molecules, physiological parameters, *etc.* can be realized with high sensitivity, which greatly helps the development of life sciences, biomedicine, clinical medicine and so on. On the other hand, researchers have devised a series of surface modified PLMs for autofluorescence-free and long-term bioimaging. And PLMs-based molecular imaging, cellular imaging, and tumor imaging are playing important roles in diagnosis and treatment of diseases, especially cancers as we mentioned above.

Although modified PLMs have been widely investigated and proved to be promising alternatives for traditional fluorescent materials, there are still many challenges ahead. Like other optical probes, collection of persistent luminescence signals relies on various large-scale and expensive instruments. In this condition, developing point-of-care methods such as PLMs-based lateral flow assay to simplify the acquisition of signals has become one of the most important directions in recent years, but they are still in their infancy and further efforts are needed to improve the detection efficiency and lower the cost. Until now, various methods have been developed to synthesize and modify PLMs of diverse properties. However, there is still a long way to achieve the goal of "top-down" synthesis, denoting the design and synthesis of materials under the guidance of a clear mechanism. Furthermore, an energy transfer process might happen from PLMs to modifiers and thus reduce or quench the luminescence,[87-88] which could lower the sensitivity of biosensing and bioimaging. For example, Zhang *et al.* reported that polypyrrole modification can reduce the luminescent intensity of Cr^{3+}-doped zinc gallogermanates.[87] These discoveries demonstrate that the influence of surface modification on the luminescent intensity of PLMs should be taken into account. On the other hand, it is necessary to make the synthetic process of PLMs green and low consumed and many recently developed synthetic methods such as microbial synthesis or biosynthesis is helpful to achieve the goal.[89] With the development of biomedical and life science, existing approaches for

surface modification is hard to meet the increasing demand of smarter PLMs-based nanoprobes in practical applications, such as lower toxicity and better selectivity, and hence new surface modification methods are urgently needed to obtain better performance of PLMs when being applied to biomedicine and clinical medicine. Last but not least, as the unique advantages that were introduced above, it can be foreseen that surface modified-PLMs might play an irreplaceable role in some important biological fields in the future. For example, monitoring of cancer cells activity and toxins or nutrient substances levels in the living body for a long time and imaging-guided therapy without continuous *in situ* external excitation to avoid possible overheating and tissue damage can be realized by surface modified-PLMs. And these studies will also greatly motivate the development of life science, biomedicine and other vital areas of focus.

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