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Autofluorescence-free chemo/biosensing in complex matrixes based on persistent luminescence nanoparticles

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ABSTRACT

Persistent luminescence nanoparticles (PLNPs), also called long-lasting afterglow nanoparticles, are magical materials that can emit long-lasting luminescence after excitation ceases. Moreover, the luminescence can be reactivated under appropriate excitation light. Such excellent optical nature enables the detection of persistent luminescence with no need for in-situ continuous excitation, thereby effectively eliminating autofluorescence interference and scattering light from complex matrixes. PLNPs, therefore, have become emerging optical materials in biological applications with bright prospect. In this review, we summarize the recent progress in autofluorescence-free chemo/biosensing, and highlight the design strategies of PLNPs-based sensors. In addition, we also make perspective on opportunities and challenges for further development in this field.

1. Introduction

Optical sensing has received increasing attention due to its inherent merits of short response time, excellent sensitivity, easy operation and low cost [1]. During the past decades, various optical materials have been designed to meet the growing demands of rapid, real-time and in-situ detection and sensing [2–4]. However, traditional optical assay based on organic fluorescent probe or inorganic fluorescent nanoparticles often suffers interference from autofluorescence and scattering light under continuous external excitation [5] as well as the photobleaching of organic fluorophores [6].

Persistent luminescence nanoparticles (PLNPs), also known as long-lasting afterglow nanoparticles, have emerged as a new generation of optical materials for autofluorescence-free detection and sensing due to the inherent merits of no need for in-situ excitation and persistent luminescence (PL) renewability [5,7–9]. PL, a well-known magical optical phenomenon, depends on the storage of the excitation energy by holes and electron traps, followed by slow release of the energy in the forms of photonic emission, which can last for a long period of time (minutes, hours or even days) [9–11]. The excellent PL nature of PLNPs enables the detection of PL after excitation ceases and short-lived autofluorescence signals decays completely to eliminate interference of autofluorescence and scattering light in accompany with the remarkable improvement of signal-to-noise ratio (SNR) and sensitivity, making them attractive for autofluorescence-free chemo/biosensing in complex matrixes, bioimaging or even theranostics [12–16].

Several excellent review articles on the synthesis and applications of PLNPs have been published so far [12–17]. For example, Qiu's group [13] systematically summarized the preparation method, characterization, PL mechanisms, materials system and the applications (e.g. displays, safety signs, optical storage, biomedical imaging, photocatalysis and solar cell) of PLNPs. Yan and co-workers [14] provided a systematic summary about their achievements in the application of PLNPs-based nanoprobes (from biosensing/bioimaging to theranostics). However, it is hard to find a comprehensive review on autofluorescence-free detection and sensing based on PLNPs in complex matrixes. Hence, this review focuses on the recent progress in autofluorescence-free detection and chemo/biosensing with emphasizing the strategies for constructing high sensitive and selective PLNPs-based sensors. It will

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draw great interests of the readers not only because this review covers the current situation of PLNPs-based sensor but also shows the problems and challenges as well as the future perspectives in this field.

2. Detection and biosensing based on resonance energy transfer

Föster resonance energy transfer (FRET) has attracted much attention in the application of detection and chemo/biosensing [2,18]. To be emphasized, resonance energy transfer process with long-lasting afterglow materials as the donor (also called afterglow resonance energy transfer (ARET) or luminescence resonance energy transfer (LRET)) could subtly overcome the autofluorescence interference from the complex matrixes caused by in-situ excitation, leading to high SNR and selectivity [19,20]. In this section, we systematically summarized PLNPs-based FRET platforms for their applications in sensing of diverse analytes.

2.1. Detection and biosensing of tumor biomarkers

Early diagnosis is the key to efficient treatment of various diseases [21]. Meanwhile, change at molecular level often occurs at the early stages of the diseases [22]. Hence, the development of sensitive and convenient methods for quantitative analysis and real-time sensing of biomarkers (such as proteins, enzymes, nucleic acids, small molecules etc.) in serum and cellular level is of great importance.

α-Fetoprotein (AFP) is a typical serum marker of hepatocellular carcinoma (HCC) [5,23]. The up-regulation of serum levels of AFP is closely associated with chronic active hepatitis, cirrhosis as well as the rapid growth of liver cancer cell [23]. Thus, the detection of AFP levels in serum is of great significance in early diagnosis of HCC. Yan's group [5] developed functional PLNPs-based FRET system for biosensing of AFP in serum samples and living cells with no need for in situ excitation. $Ca_{1.86}Mg_{0.14}ZnSi_2O_7:Eu^{2+},Dy^{3+}$ PLNPs with stable PL in the duration of 30–180 min after ceasing excitation were prepared and used as the signal element to offer a reliable time window for the background-free detection of AFP. Then, a luminescence-silent PLNPs-based nanoprobe based on FRET process was designed and constructed via the electrostatic assembling of polyethyleneimine (PEI) functionalized PLNPs (PEI-PLNPs) and AFP antibody-coated gold nanoparticles (Ab-AuNPs) for high selective and sensitive detection of AFP (Fig. 1). Ab-AuNPs seceded from PEI-PLNPs accompanied with obvious activation of PL upon addition of AFP because the strong and specific affinity of AFP to the antibody triggers the competition of AFP for Ab-AuNPs. The as-prepared FRET nanoprobe not only realized highly selective, sensitive and background-free quantitation of AFP with the detection limit (LOD) of 0.41 μg L^{-1}, but also successful monitoring of the AFP excreted during cell growth. The pioneering PLNPs-based biosensing breaks a new pathway for designing high sensitive and background-free nanoprobes.

Fibroblast activation protein-alpha (FAPα), a cell surface glycoprotein, universally expressed in stromal fibroblasts of human epithelial cancers, but scarcely expressed in normal tissues. Besides, FAPα plays an important role in cell proliferation, invasion and metastasis [19,24]. Wang et al. [19] reported an ARET sensor based on functionalized PLNPs for quantitative analysis and imaging of FAPα (Fig. 2). Mercaptopropionic acid and Au nanoparticles-decorated $Cr^{3+}_{0.004}:ZnGa_2O_4$ PLNPs ($Cr^{3+}_{0.004}:ZnGa_2O_4$@MPA@Au) with 695 nm emission served as the ARET donor. Cy5.5 probe with absorbance of 550–750 nm acted as the acceptor owning to the strong overlap with the emission of PLNPs. Meanwhile, a FAPα-specific peptide sequence (KGPNQC) was employed as the linker between the PLNPs and Cy5.5 probe to build the ARET system. In the presence of FAPα, the PL of $Cr^{3+}_{0.004}:ZnGa_2O_4$@MPA@Au was restored

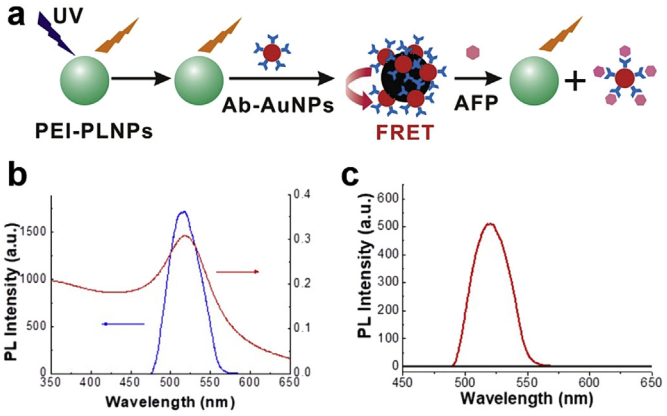

Fig. 1. High selective and background-free detection of AFP using PLNPs-based FRET system. (a) Schematic illustration of the PLNPs-based FRET system for specific recognition of AFP. (b) Absorption spectra and photoluminescence emission spectra of Ab-AuNPs (red curve) and PEI-PLNPs (blue curve), respectively. (c) Photoluminescent spectra of a serum sample with detectable AFP before (black line) and after (red curve) addition of the as-prepared FRET nanoprobe (3 g L^{-1}) without excitation. Reprinted with permission from ref. [5]. Copyright 2011 American Chemical Society.

due to the inhibition of the ARET process as a result of the cleavage of peptide with FAPα. The as-prepared PLNPs-based ARET sensor was not only employed to detect FAPα with the linear range from 0.1 to 2.0 mg L^{-1} and LOD of 11 μg L^{-1}, but also applied for monitoring the FAPα in FAPα-positive cells (MDA-MB-435 and U87MG cells) with the spiked recoveries of 95.6–103%. This strategy shows great potential in bioanalytical applications due to its great merits of high sensitivity, lower LOD, and strong anti-interference capability.

Tan's group [10] reported a lysozyme binding aptamer (LBA) guided Zn_2GeO_4:Mn persistent luminescence nanorods (ZGO:Mn) for autoflourescence-free detection of lysozyme in serum (Fig. 3). LBA-modified ZGO:Mn (ZGO:Mn-LBA) served as the photoluminescence group and FRET donor due to its tunable length and strong PL after cessation of excitation. Meanwhile, DNA labeled with black-hole-quencher (BHQ-DNA) acted as acceptor to quench the PL of ZGO:Mn-LBA via DNA hybridization. The addition of lysozyme destroyed the FRET system, thus lighted up the PL of ZGO:Mn-LBA due to the desorption of BHQ-DNA from the ZGO:Mn-LBA as a result of the conformational change of LBA (folds into a unique 3D structure). The excellent PL "turn-on" property enables the nanoprobe to monitor lysozyme in serum samples from patients without autofluorescence interference. The quantification results were in good accordance with those obtained by clinical ELISA, suggesting the great value of this nanoprobe in the application of clinical samples.

Integrating FRET assay with ratiometric luminescent detection is helpful to further improve the accuracy and sensitivity. Hence, Yan and co-workers [25] subsequently exploited a PLNPs-based FRET immunoassay with ratiometric luminescence response for high selective and sensitive detection of prostate-specific antigen (PSA, the most sensitive biomarker of prostate cancer [25,26]) (Fig. 4). The PLNPs mentioned above ($Ca_{1.86}Mg_{0.14}ZnSi_2O_7:Eu^{2+},Dy^{3+}$) modified with mouse monoclonal PSA antibody (PS6) (designated as PLNP-PS6) was chosen as signal element and the energy donor due to its excellent PL features. Rhodamine B (RhB) pre-functionalized with 8A6 (another mouse monoclonal PSA antibody) (designated as RhB-8A6) was employed as the acceptor to build the ratiometric immunoassay system owning to the maximum overlap of its absorption spectrum and the emission spectrum of PLNP-PS6. The up-regulates in the concentration of PSA resulted in an increase of the ratio of the fluorescence intensity of RhB (at 585 nm) to the phosphorescence intensity of PLNP (at

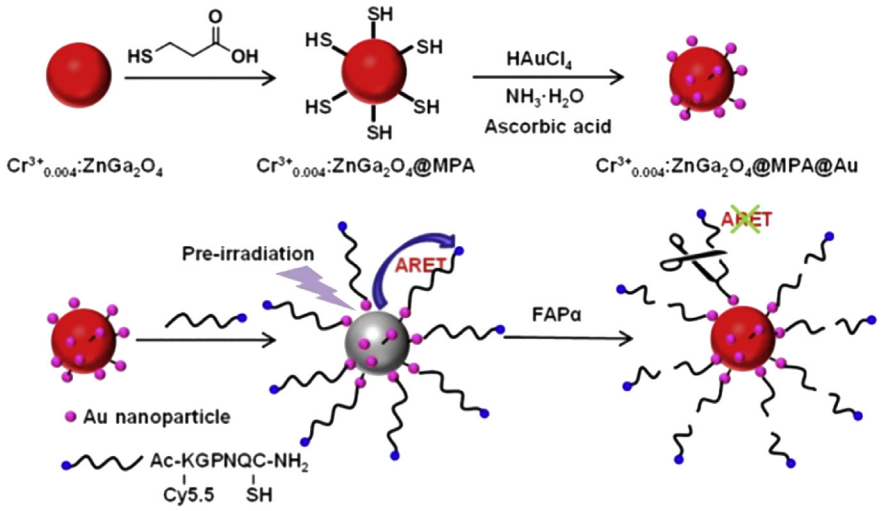

Fig. 2. Illustration of the design and synthesis of $Cr^{3+}_{0.004}$:$ZnGa_2O_4$@MPA@Au for the specific recognition of FAPα. Reprinted with permission from ref. [19]. Copyright 2018 American Chemical Society.

524 nm) as the shortened distance between PLNP-PS6 and RhB-8A6 triggered the FRET effect as a result of the specific interaction of PSA with PS6 and 8A6. The excellent PL features of PLNPs and the specific antigen–antibody recognition behavior endow them great potential for highly sensitive and selective detection of PSA in biological samples (such as serum and cell extracts) without autofluorescence interference. It is worth mentioning that the strategy for the design of FRET immunoassay based on PLNPs is easily to extend to the detection of other biomarkers by simply replacing the antibodies.

2.2. Detection and biosensing of bioactive molecules

Bioactive molecules play crucial roles in numerous biochemical and physiological functions, cell signaling and neurotransmission, which are often involved in both various disease and human health. Thus, it is of great significance to develop effective methods for the specific detection of biomolecules.

Ascorbic acid (AA) is an essential micronutrient needed in numerous biochemical and physiological functions. Besides, it is also well-known as an important water-soluble antioxidant which can quickly scavenge lots of reactive species and effectively avoid oxidative damage of other biomolecules [27]. Tang's group [28] presented cobalt oxyhydroxide (CoOOH)-modified PLNPs for highly selective and point-of-care (POC) detection and imaging of AA based on specific reaction of AA and CoOOH. $Sr_2MgSi_2O_7$:Eu, Dy PLNPs were used as the photoluminescence unit due to its long-lasting afterglow nature, and CoOOH nanoflakes were employed as both recognition unit and quencher owing to its specific instantaneous reaction with AA and strong absorption spectrum overlap with the emission spectrum of the PLNPs. The photoluminescence of PLNPs was significantly quenched by CoOOH via FRET effect. Meanwhile, the quenching effect was reversed by the

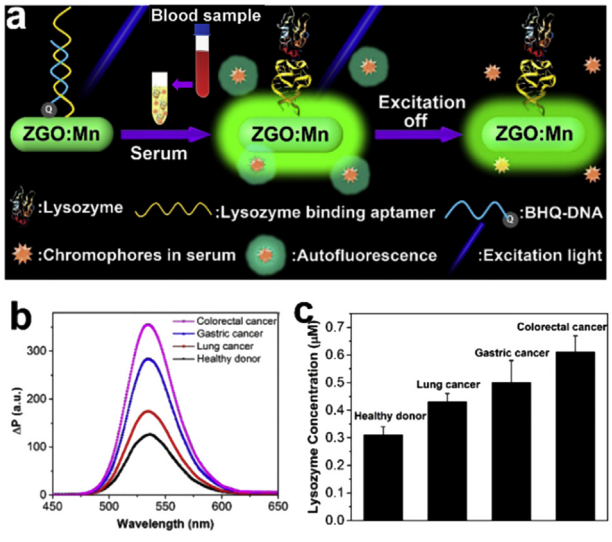

Fig. 3. (a) Schematic illustration of autofluorescence-free ZGO:Mn-based lysozyme biosensing of the serum samples from cancer patients. (b) Response of the as-prepared ZGO:Mn-based nanoprobe to different kinds of serum samples. (c) Concentrations of lysozyme in different kinds of serum determined by the as-prepared ZGO:Mn-based nanoprobe. Reprinted with permission from ref. [10]. Copyright 2017 American Chemical Society.

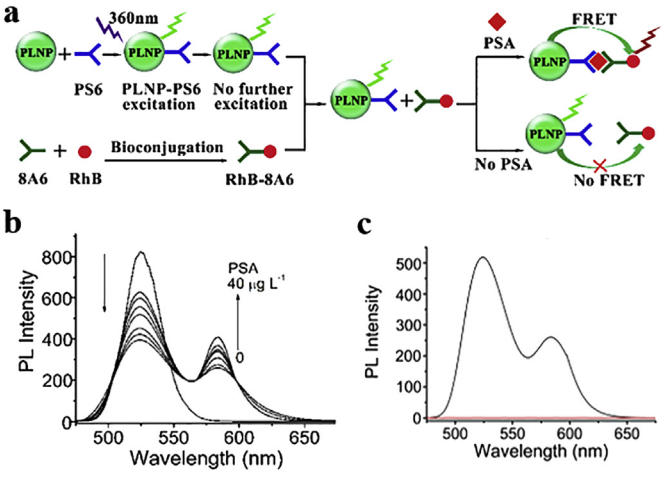

Fig. 4. (a) Schematic illustration of the design of PLNPs-based FRET immunoassay for ratiometric luminescence detection of PSA. (b) Change of PL intensity of PLNP-PS6 (4.65 g L^{-1})/RhB-8A6 (4.5 g L^{-1}) upon different concentration of PSA. (c) PL spectra of a serum sample spiked with 10 g L^{-1} PSA in the presence (black curve) or absence (red line) of PLNP-PS6 (4.65 g L^{-1}) and RhB-8A6 (4.5 g L^{-1}) without external excitation. Reproduced from Ref. [25] with permission from The Royal Society of Chemistry.

addition of AA as a result of the reduction of CoOOH to Co^{2+}. Thus, the CoOOH-modified PLNPs were successfully applied for highly selective and background-free detection and imaging of AA with the linear range of 1–100 μM and LOD of 0.59 μM.

Dopamine (DA) plays a crucial role in hormonal, central nervous and cardiovascular systems. Excessive DA in the brain often causes pleasurable feelings or even euphoria [29], deficient DA in neurons involves with neurological disorders etc [30,31]. Lv and co-workers [31] reported a persistent luminescence microspheres-based probe for selective detection and imaging of DA. $SrMgSi_2O_6:Eu_{0.01},Dy_{0.02}$ microspheres, synthesized via a simple template method and excited by sunlight, were employed as the photoluminescence and recognition unit to achieve a high SNR detection. Then, a convenient detection platform for DA was established based on "turn-off" of the PL emission due to the electrostatic interaction between the alkaline persistent luminescence microspheres and DA-quinine, the oxidation product of DA. This strategy was not only employed to selectively detect DA in biological fluids with LOD of 0.78 μM, but also used to image and monitor of DA in human urine with quantitative recovery (99.6–102.5%).

The fluctuation in the level of biothiols (such as cysteine (Cys), homocysteine (Hcy) and glutathione (GSH)) is closely associated with psoriasis, leukocyte loss, liver damage and cancer [32–34]. Hence, Lv's group [35] presented another persistent luminescence nanoprobe for "turn-on" PL imaging of biothiols in biological fluids based on an electron transfer process (Fig. 5). The turn-off PL platform was fabricated using graphitic carbon nitride (g-C_3N_4) PLNPs as donor and silver ion (Ag^+) as acceptor via electron transfer process. The ultrastrong PL of G-C_3N_4 nanosheets fabricated via the pyrolysis of guanidine hydrochloride under ambient atmospheric conditions endows the detection without need for external excitation. The surface adsorption of Ag^+ onto g-C_3N_4 materials made the original PL of g-C_3N_4 turn off, while obvious PL of g-C_3N_4 materials was lighted up with biothiols due to the inhibition of the interactions between g-C_3N_4 and Ag^+ by biothiols. The excellent PL "turn-on" property enables the nanoprobe for high specific, sensitive and autofluorescence-free detection of Cys, Hcy and GSH with low LODs of 6.4, 8.1, and 9.6 nM, respectively. They also explored the nanoplatform to monitor the biothiols in plasma, human urine and cell lysates, and demonstrated its great potential in the sensing of biological systems.

Tang and co-workers [34] also presented a novel nanoprobe for external excitation- and background-free detection of GSH based on manganese dioxide (MnO_2)-encapsulated PLNPs. $SrMgSiO_7$ PLNPs were prepared and acted as the photoluminescence unit, and then further coating with MnO_2 on the surface PLNPs to build the luminescence-silent platform for the specific recognition of GSH. The PL of the as-prepared nanoplatform was obviously recovered by the addition of GSH, owning to the specific reduction of MnO_2 by GSH in accompany with the inhibition of MnO_2-induced FRET effect. The selective "turn-on" nature of PL and no need for external excitation ensures the nanoprobe as a promising platform for selective and sensitive detection and imaging of GSH.

Cyanide ion (CN^-) commonly exits in the membrane of the mitochondria of eukaryotic cells, and it can inhibit the activity of enzyme cytochrome c oxidase [36,37]. Considering the importance of CN^-, Lv's group [37] reported a LRET platform for CN^- detection and sensing based on surface-modified PLNPs. $ZnGa_2O_4:Mn^{2+}$ ($ZGO:Mn^{2+}$) PLNPs and chromophores (DEHSPI) were employed as two main moieties for the LRET platform. $ZGO:Mn^{2+}$ PLNPs acted as the energy donor due to its merits of excellent PL properties. DEHSPI, a chromophore with tunable light absorption by CN^-, served as the energy acceptor as well as recognition unit. Electrostatic assemble of DEHSPI on the surface of carboxyl functionalized PLNPs resulted in a PL-silent system due to the LRET process. The selective inhibition of the LRET process induced by CN^- lighted up the PL signal. The PLNPs-based nanoprobe exhibits outstanding recognition and background-free sensing capacity for CN^- (LOD of 0.11 μM). Moreover, the nanoprobe offered excellent analytical performance and low cytotoxicity for CN^- imaging in living cells. It is worth mentioning that this PLNP-based LRET platform can be expanded to detect and sense other analytes via modulate the recognition element, holding great promise for the detection of CN^- or other analytes in various pathological processes.

2.3. Detection and biosensing of pathogenic microorganism

Real-time monitoring and early warning of pathogenic microorganisms which may do great harm to human health is of great importance in modern society. For example, aflatoxins are well-known highly hepatotoxic, carcinogenic, and mutagenic food-borne toxins [38,39]. Wang and co-workers [40] designed a luminescence-activatable PLNPs–CuS hybrid nanoplatform for targeted imaging of Aflatoxin B1 (AFT B1, the most common aflatoxin) (Fig. 6). $Zn_{1.25}Ga_{1.5}Ge_{0.25}O_4:0.5\%Cr^{3+}$, $2.5\%Yb^{3+}$, $0.25\%Er^{3+}$ (ZGGO) PLNPs reported by Yan's group [41] were used as a near-infrared (NIR) phosphorescence unit to ensure background-free bioimaging due to their unique merits of no need for in situ excitation, super-long afterglow and PL renewability. Meanwhile, CuS nanoparticles were employed as a quencher owing to the strong overlap between their broad absorption and the phosphorescence emission of the PLNPs. The as-prepared PLNPs and CuS were further functionalized with AFT B1 specific aptamer and its complementary ssDNA to build the PLNPs–CuS-based PL-silent nanoprobes based on DNA hybridization. The presence of target AFT B1 induced the separation of PLNPs with CuS and accompanied with the obvious recovery of PL owing to the high affinity of AFT B1 to the aptamer, resulting in the breakup of the DNA hybrid. This activatable hybrid nanoprobe was successfully applied for the determination and imaging of AFT B1 both in cells and *in vivo* with high sensitivity and specificity.

2.4. Detection and biosensing of pollutants

Real-time detection and quantitative analysis of pollutants with high selectivity and sensitivity is of great importance for human health, environmental safety as well as security screening [42]. Afterglow-based detection methods present excellent superiority, such as reduced light scattering, less background interference and easier operation, compared to the fluorescence-based measurements, enabling PLNPs to be a promising platform for the quantitative analysis and biosensor of pollutants. Hu's group [42] constructed a label-free photoluminescence "turn-off" sensor based on $Sr_2Al_{14}O_{25}:Eu^{2+}$, Dy^{3+} PLNPs for sensitive and selective detection of two kinds of organic pollutants of antibiotics and 2,4,6-trinitrophenol (TNP). The presence of antibiotic and TNP resulted in the luminescence quenching of PLNPs due to the wide overlap between the absorption of these pollutants and the phosphorescence emission of the PLNPs. Hence, selective sensing and quantitative analysis platform of the antibiotic and TNP was easily built under the optimal conditions. The nanoprobe was successfully applied for the detection of TNP and antibiotic with the LOD of 10 nM and 5 nM, respectively. Besides, the biosensor was also explored to monitor these pollutants in real samples (milk and Dianchi Lake water) and test papers without background interference. The easy-to-use sensing platform provides a powerful tool for POC assay of organic pollutants.

3. Detection and biosensing based on time-resolved fluorescence resonance energy transfer

Time-resolved fluorescence resonance energy transfer (TR-FRET) assay, which integrates the features of time-resolved

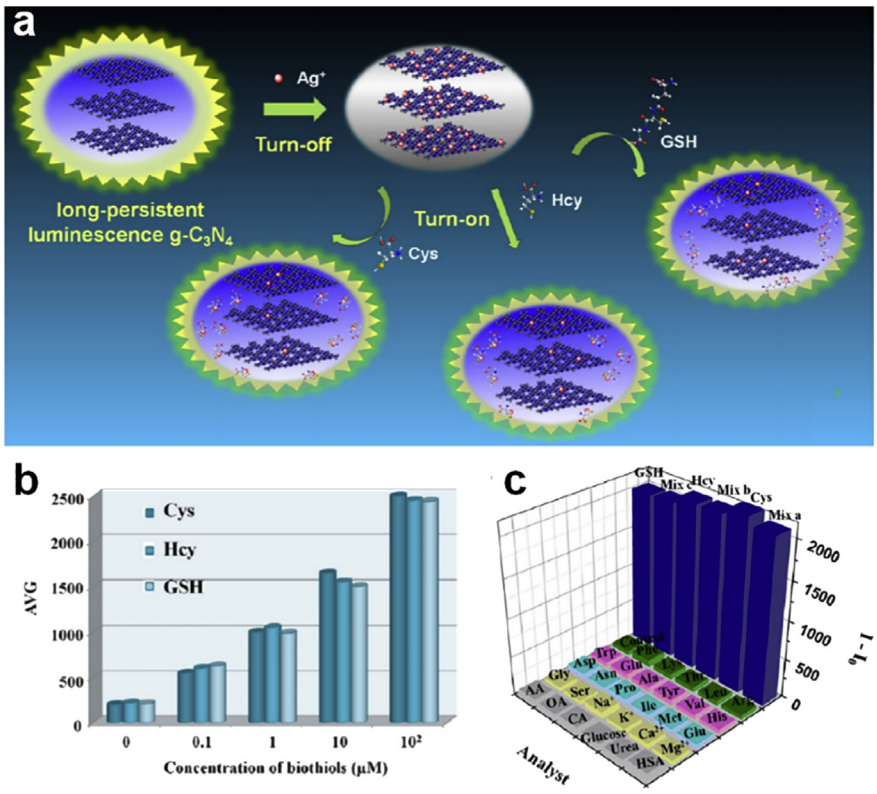

Fig. 5. (a) Schematic illustration of the design of Ag^+-g-C_3N_4 nanosheets for biothiols imaging. (b) Average intensity of Ag^+-g-C_3N_4 (g-C_3N_4 (1 mg mL^{-1}) with Ag^+ (100 μM)) with various concentrations of biothiols (0–100 μM) under a photon accumulation for 1 min. (c) The PL responses of the Ag^+-g-C_3N_4 to Cys, Hcy, GSH (5 μM), 20 essential amino acids (5 mM, respectively), small molecules (containing glucose, citric acid, oxalic acid and ascorbic acid (50 μM, respectively)), metal ions (including Mg^{2+}, Ca^{2+}, K^+ and Na^+ (5 mM, respectively)), HSA (25 mg L^{-1}) and urea (1 mM). All of the above substances except GSH and Hcy (Mix a); except GSH and Cys (Mix a); except Cys and Hcy (Mix c). Reprinted with permission from ref. [35]. Copyright 2013 American Chemical Society.

fluorescence (TRF) and FRET can reduce the autofluorescence and short-lived background luminescence interference, has emerged as attractive strategy in highly sensitive and selective, background-free optical detection and imaging [43–45]. Integrating long-lasting afterglow materials into TR-FRET assay as built-in light source instead of the traditional pulsed excitation laser shows more superior advantages of convenient operation, low requirement for equipment and non-background luminescence interference [46,47].

Ju's group [46] employed PLNPs to build TR-FRET platform for the detection of caspase-3, microRNA-21 and platelet-derived growth factor (PDGF), respectively (Fig. 7). Three kinds of "on-off", "off-on" and "on-on" PLNPs-based TR-FRET nanoprobes were designed and prepared by conjugating PLNPs with fluorescein isothiocyanate (FITC)-labeled caspase-3 specific peptide or DNA. The "on-off" strategy for the detection of caspase-3 resulted from the detachment of FITC from PLNPs by the enzymatic cleavage reaction accompanied by the inhibition of the FRET process from PLNPs to FITC. In contrast, the 'off-on' switch or the "on-on" TR-FRET strategy was generated by the combination of FITC with PLNPs because the sandwich hybridization among miRNA-21, DNA1 and DNA2 or the recognition of the FITC-labeled aptamer to target protein, respectively. Each of the strategy shows great potential for the detection of caspase-3, nucleic acids and proteins

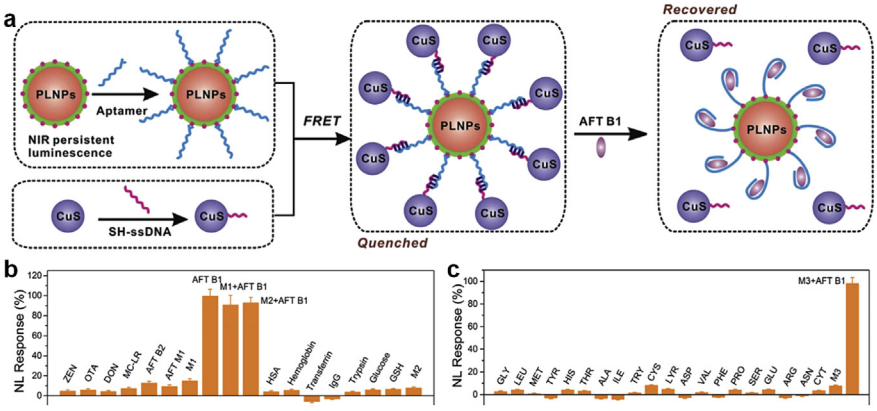

Fig. 6. (a) Schematic illustration of the design of luminescence-activatable PLNPs-CuS hybrid nanoplatform for the sensing of aflatoxin. (b and c) Specificity determination of AFT B1 based on the PLNPs-CuS hybrid nanoplatform. Reproduced from Ref. [40] with permission from The Royal Society of Chemistry.

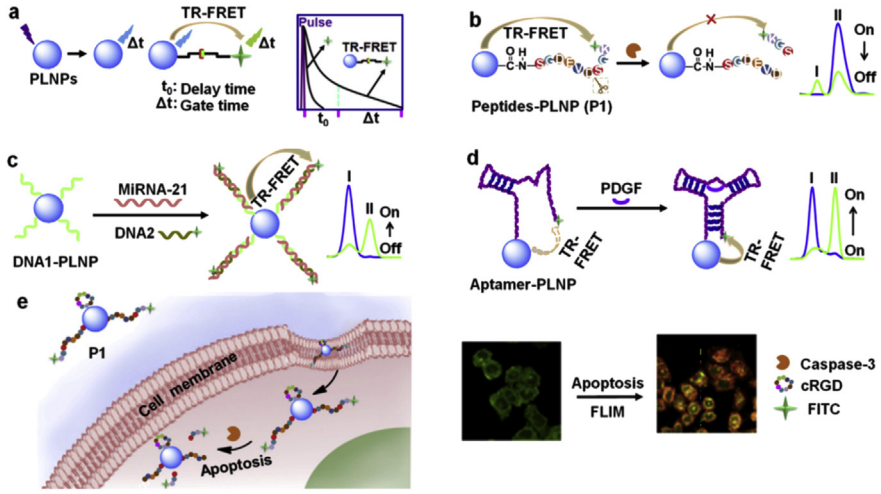

Fig. 7. Schematic illustration of (a) PLNPs-based TR-FRET principle, (b, c and d) TR-FRET platform for caspase-3 protease, miRNA-21 and PDGF protein, respectively. I and II represent TRF signals of PLNPs (468 nm) and FITC (520 nm), respectively. Blue and green curves represent the TRF curves before and after responding with the corresponding target, respectively. (e) Lifetime imaging of intracellular caspase-3 during cell apoptosis based on "on-off" TR-FRET strategy by FLIM. Reprinted from biomaterials (ref. [46]), Copyright (2015), with permission from Elsevier.

with a wide linear detection range and a low LOD. The "on-off" TR-FRET strategy was also employed to monitor caspase-3 during cell apoptosis via fluorescence lifetime imaging microscopy. PLNPs-based TR-FRET strategy provides a new perspective for the design of sensitive sensing and dynamically tracking platform.

Yan's group [47] reported a ratiometric absorption (Ratio-Abs) and TR-FRET dual-signaling nanoplatform based on functionalized gold nanoparticles (AuNPs) and PLNPs for high-throughput sequential detection of L-cysteine (L-Cys) and insulin (Ins) (Fig. 8). PLNPs and AuNPs were employed as two signaling units due to the PL nature of PLNPs as well as tunable absorption and high molar extinction coefficient of AuNPs. Insulin binding aptamer (IBA) and thiol-functionalized partial complementary sequence (SH-CS) served as functional group and recognition element to obtain IBA functionalized PLNPs (PLNP-IBA) and SH-CS modified AuNRs (AuNP-CS), the core of dual-signaling nanoplatform. The presence of L-Cys induced the aggregation of AuNP-CS accompanied by the significant red shift in the absorption band of AuNP-CS, a Ratio-Abs nanoprobe based on AuNP-CS for the detection of L-Cys was thus successfully constructed. Meanwhile, the TR-FRET detection of Ins was easily realized based on the self-Assembly of PLNP-IBA and aggregated AuNP-CS. The interaction between IBA and CS led to PL quenching of PLNPs due to the FRET between PLNP-IBA and aggregated AuNP-CS. However, the PL quenching of PLNPs was obviously recovered in the presence of Ins due to the inhibition of TR-FRET as a result of the strong interaction between Ins and IBA. The dual-signaling nanoplatform not only have achieved high selective determination of L-cysteine and Ins with the liner range of 10 nM-5.5 μM and 12pM-3.44 nM, and the LOD of 2.2 nM and 2.06 pM, respectively, but also realized high-throughput sequential and background-free detection of L-cysteine and Ins in human serum. The present strategy opens a new approach for designing high-throughput, high selective and multi-detection assays of biological sample.

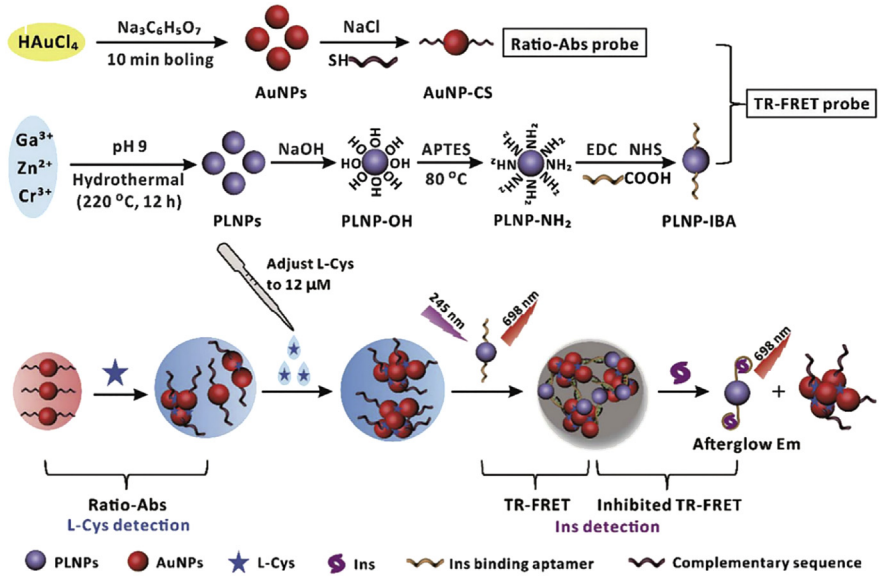

Fig. 8. Schematic illustration of the design of Ratio-Abs and TR-FRET dual-signaling nanoplatform for high-throughput sequential detection of L-Cys and Ins. Complementary sequence represents partial complementary sequence of Ins binding aptamer (IBA). Reproduced from Ref. [47] with permission from The Royal Society of Chemistry.

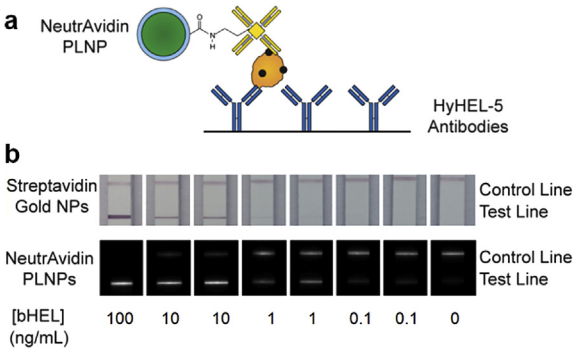

Fig. 9. (a) Schematic illustration of test line showing NeutrAvidin PLNP bound to bHEL captured by *anti*-HEL antibodies. (b) LFA strips showing bHEL serial dilutions with duplicates and detection with Streptavidin gold nanoparticles (up) and NeutrAvidin PLNPs (bottom). Reprinted with permission from ref. [50]. Copyright 2014 American Chemical Society.

4. Detection and biosensing based on lateral flow assays

Lateral flow assays (LFA) have emerged as promising assay methods for POC detection and sensing, whose typical application is home pregnancy tests [48]. Fluorescent probes/nanoparticles have been gradually used in LFAs and achieved wider dynamic range and higher sensitivity than the conventional AuNPs [49]. PLNPs is expected to be a better alternative to AuNPs due to its excellent luminescence properties, which can simply eliminate the photobleaching of fluorescent probes, autofluorescence interference and the complexity of the readout device from the requirement of continuous excitation [50]. Willson's group [50] first reported the use of PLNPs as reporters in LFAs with a model analyte (biotinylated lysozyme) (Fig. 9). Small-sized $SrAl_2O_4:Eu^{2+},Dy^{3+}$ PLNPs, small enough to move in the LFAs membranes, were obtained by wet milling and differential sedimentation from commercial larger-particle strontium aluminate PLNPs. Further encapsulation with silica and functionalization with NeutrAvidin to obtain the water-stabilized PLNPs, used as reporters. Nitrocellulose strips were marked with immobilized HyHEL-5 monoclonal anti-lysozyme antibodies at the test line, and labeled biotinylated-bovine serum albumin at the control line. The LOD of the NeutrAvidin PLNPs (below 100 pg mL^{-1}) was approximately an order of magnitude lower than that of AuNRs. These results indicate that PLNPs are promising indicators for LFAs and other POC tests.

Another heterogeneous assay based on PLNPs was shown by Chen and co-workers [11] (Fig. 10). A modified solvothermal liquid–solid-solution method was developed for the preparation of high-performance $ZnGa_2O_4:Cr^{3+}$ PLNPs with the unique merits of mono-dispersity, LED-activated NIR phosphorescence emission and flexible for bioconjugation. Oleic acid was employed as the surfactant not only to avoid the aggregation of PLNPs but also to endow the excellent flexibility of PLNPs for surface functionalization and bioconjugation. The mechanism study showed that the afterglow decay of the PLNPs was contributed by quantum tunneling and thermal activation mechanisms while the LED-activated afterglow intensity and lasting time were controlled by quantum tunneling. The as-prepared $ZnGa_2O_4:Cr^{3+}$ PLNPs was further modified with biotin for background-free heterogeneous detection of the avidin protein with sensitivity and selectivity (LOD of 150 pM).

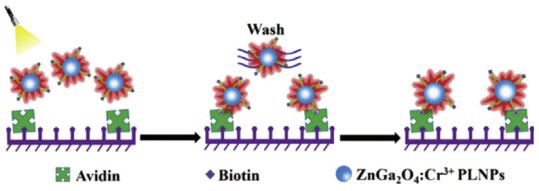

Fig. 10. Schematic illustration of the heterogeneous assay of avidin based on PLNPs. Reproduced from Ref. [11] with permission from The Royal Society of Chemistry.

5. Conclusion

PLNPs are a new generation of optical materials for negligible interference of scattering light and autofluorescence-free chemo/biosensing due to the unique merits of no need for in situ excitation and PL renewability. This review has provided the state of the art on PLNPs-based autofluorescence-free detection and sensing in complex matrixes. Various engineering strategies have been employed to build PLNP-based sensors, and highly selective and superior SNR chemo/biosensing in complex matrixes has been achieved.

Although great progress has been made, the development of PLNPs-based sensors for complex matrixes is only in its infancy. There is still great room to be explored in this direction. Firstly, high performance PLNPs with small-sized, mono-dispersed, ultrabright initial phosphorescence and long PL lifetime are urgent needed. Secondly, novel PLNPs with multi-wavelength emissions are highly desired to realize simultaneous multi-element analysis or ratiometric sensing. Thirdly, Universal functionalization strategy remains unexplored. Last but not least, rapid and accurate measuring methods are necessary to cater to the slow-decaying signals. In a word, great efforts should be taken to improve the chemo/biosensing performance of PLNPs-based platform to meet the growing needs of POC assay.

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References

[1] X.C. Sun, Y. Lei, Fluorescent carbon dots and their sensing applications, TrAC Trends Anal. Chem. 89 (2017) 163–180.
[2] P. Das, A. Sedighi, U.J. Krull, Cancer biomarker determination by resonance energy transfer using functional fluorescent nanoprobes, Anal. Chim. Acta 1041 (2018) 1–24.
[3] H.S. Wang, Development of fluorescent and luminescent probes for reactive oxygen species, TrAC Trends Anal. Chem. 85 (2016) 181–202.
[4] J. Soleymani, M. Hasanzadeh, M.H. Somi, A. Jouyban, Nanomaterials based optical biosensing of hepatitis: recent analytical advancements, TrAC Trends Anal. Chem. 107 (2018) 169–180.
[5] B.-Y. Wu, H.-F. Wang, J.-T. Chen, X.-P. Yan, Fluorescence resonance energy transfer inhibition assay for α-fetoprotein excreted during cancer cell growth using functionalized persistent luminescence nanoparticles, J. Am. Chem. Soc. 133 (4) (2011) 686–688.
[6] U. Resch-Genger, M. Grabolle, S. Cavaliere-Jaricot, R. Nitschke, T. Nann, Quantum dots versus organic dyes as fluorescent labels, Nat. Methods 5 (9) (2008) 763–775.
[7] P.L. Suarez, M. Garcia-Cortes, M.T. Fernandez-Arguelles, J.R. Encinar, M. Valledor, F.J. Ferrero, J.C. Campo, J.M. Costa-Fernandez, Functionalized phosphorescent nanoparticles in (bio)chemical sensing and imaging - a review, Anal. Chim. Acta 1046 (2019) 16–31.
[8] A. Abdukayum, J.-T. Chen, Q. Zhao, X.-P. Yan, Functional near infrared-emitting Cr^{3+}/Pr^{3+} co-doped zinc gallogermanate persistent luminescent nanoparticles with superlong afterglow for *in vivo* targeted bioimaging, J. Am. Chem. Soc. 135 (38) (2013) 14125–14133.
[9] Z.W. Pan, Y.-Y. Lu, F. Liu, Sunlight-activated long-persistent luminescence in the near-infrared from Cr^{3+}-doped zinc gallogermanates, Nat. Mater. 11 (2012) 58–63.

[10] J. Wang, Q. Ma, W. Zheng, H.Y. Liu, C.Q. Yin, F.B. Wang, X.Y. Chen, Q. Yuan, W.H. Tan, One-dimensional luminous nanorods featuring tunable persistent luminescence for autofluorescence-free biosensing, ACS Nano 11 (8) (2017) 8185–8191.
[11] Z.H. Zhou, W. Zheng, J.T. Kong, W. Liu, P. Huang, S.Y. Zhou, Z. Chen, J.L. Shi, X.Y. Chen, Rechargeable and LED-activated $ZnGa_2O_4$: Cr^{3+} near-infrared persistent luminescence nanoprobes for background-free biodetection, Nanoscale 9 (20) (2017) 6846–6853.
[12] L. Liang, N. Chen, Y.Y. Jia, Q.Q. Ma, J. Wang, Q. Yuan, W.H. Tan, Recent progress in engineering near-infrared persistent luminescence nanoprobes for time-resolved biosensing/bioimaging, Nano Res. 12 (6) (2019) 1279–1292.
[13] Y. Li, M. Gecevicius, J.R. Qiu, Long persistent phosphors-from fundamentals to applications, Chem. Soc. Rev. 47 (22) (2016) 2090–2136.
[14] S.K. Sun, H.F. Wang, X.-P. Yan, Engineering persistent luminescence nanoparticles for biological applications: from biosensing/bioimaging to theranostics, Accounts Chem. Res. 51 (5) (2018) 1131–1143.
[15] J.H. Liu, T. Lécuyer, J. Séguin, N. Mignet, D. Scherman, B. Viana, C. Richard, Imaging and therapeutic applications of persistent luminescence nanomaterials, Adv. Drug Deliv. Rev. 138 (2018) 193–210.
[16] J. Wang, Q. Ma, Y. Wang, H. Shen, Q. Yuan, Recent progress in biomedical applications of persistent luminescence nanoparticles, Nanoscale 6 (13) (2017) 6204–6218.
[17] J. Xu, S. Tanabe, Persistent luminescence instead of phosphorescence: history, mechanism, and perspective, J. Lumin. 205 (2019) 581–620.
[18] S.-Y. Wang, C.-F. Wang, Y.-K. Lv, S.-G. Shen, Fabrication of fluorescent biosensing platform based on graphene oxide-DNA and their application in biomolecule detection, TrAC Trends Anal. Chem. 106 (2018) 53–61.
[19] F. Feng, X. Chen, G. j. Li, S. Liang, Z.Y. Hong, H.-F. Wang, Afterglow resonance energy transfer inhibition for fibroblast activation protein-α assay, ACS Sens. 3 (9) (2018) 1846–1854.
[20] Z. Li, S.W. Lv, Y.L. Wang, S.Y. Chen, Z.H. Liu, Construction of LRET-based nanoprobe using upconversion nanoparticles with confined emitters and bared surface as luminophore, J. Am. Chem. Soc. 137 (9) (2015) 3421–3427.
[21] B.L. Ziober, M.G. Mauk, E.M. Falls, Z.Y. Chen, A.F. Ziober, H.H. Bau, Lab-on-a-chip for oral cancer screening and diagnosis, Head Neck 30 (1) (2008) 111–121.
[22] Y. Shimizu, K. Yasui, K. Matsueda, A. Yanagisawa, K. Yamao, Small carcinoma of the pancreas is curable: new computed tomography finding, pathological study and postoperative results from a single institute, J. Gastroenterol. Hepatol. 20 (10) (2005) 1591–1594.
[23] L.X. Qin, Z.Y. Tang, Recent progress in predictive biomarkers for metastatic recurrence of human hepatocellular carcinoma: a review of the literature, J. Cancer Res. Clin. Oncol. 130 (9) (2004) 497–513.
[24] L.J. Deng, L.H. Wang, C.K. Peng, Y.B. Li, M.H. Huang, M.F. Chen, X.P. Lei, M. Qi, Y. Cen, W.C. Ye, D.M. Zhang, W.M. Chen, Fibroblast activation protein α activated tripeptide bufadienolide antitumor prodrug with reduced cardiotoxicity, J. Med. Chem. 60 (13) (2017) 5320–5333.
[25] B.Y. Wu, X.-P. Yan, Bioconjugated persistent luminescence nanoparticles for Föster resonance energy transfer immunoassay of prostate specific antigen in serum and cell extracts without in situ excitation, Chem. Commun. 51 (18) (2015) 3903–3906.
[26] J.J. Xu, W.W. Zhao, S.P. Song, C.H. Fang, H.Y. Chen, Functional nanoprobes for ultrasensitive detection of biomolecules: an update, Chem. Soc. Rev. 43 (5) (2014) 1601–1611.
[27] H.J. Cheng, L.J. Li, M.N. Zhang, Y. Jiang, P. Yu, F. Ma, L.Q. Mao, Recent advances on *in vivo* analysis of ascorbic acid in brain functions, Trac. Trends Anal. Chem. 109 (2018) 247–259.
[28] N. Li, Y.H. Li, Y.Y. Han, W. Pan, T.T. Zhang, B. Tang, A highly selective and instantaneous nanoprobe for detection and imaging of ascorbic acid in living cells and *in vivo*, Anal. Chem. 86 (8) (2014) 3924–3930.
[29] P.N. Tobler, C.D. Fiorillo, W. Schultz, Adaptive coding of reward value by dopamine neurons, Science 307 (5715) (2005) 1642–1645.
[30] B.J. Venton, R.M. Wightman, Psychoanalytical electrochemistry: dopamine and behavior, Anal. Chem. 75 (19) (2003) 414A–421A.
[31] J. Tang, Y. Su, D. Deng, L. Zhang, N. Yang, Y. Lv, A persistent luminescence microsphere-based probe for convenient imaging analysis of dopamine, Analyst 141 (18) (2016) 5366–5373.
[32] D.M. Townsend, K.D. Tew, H. Tapiero, The importance of glutathione in human disease, Biomed. Pharmacother. 57 (3–4) (2003) 145–155.
[33] H.S.J.H.S. Jung, X. Chen, J.S. Kim, J.Y. Yoon, Recent progress in luminescent and colorimetric chemosensors for detection of thiols, Chem. Soc. Rev. 42 (14) (2013) 6019–6031.
[34] N. Li, W. Diao, Y.Y. Han, W. Pan, T.T. Zhang, B. Tang, MnO_2-modified persistent luminescence nanoparticles for detection and imaging of glutathione in living cells and *in vivo*, Chem. Eur. J. 20 (50) (2014) 16488–16491.
[35] Y.R. Tang, H.J. Song, Y.Y. Su, Y. Lv, Turn-on persistent luminescence probe based on graphitic carbon nitride for imaging detection of biothiols in biological fluids, Anal. Chem. 85 (24) (2013) 11876–11884.
[36] D. Shan, C. Mousty, S. Cosnier, Subnanomolar cyanide detection at polyphenol oxidase/clay biosensors, Anal. Chem. 76 (2004) 178–183.
[37] Y. Feng, D. Deng, L. Zhang, R. Liu, Y. Lv, LRET-based functional persistent luminescence nanoprobe for imaging and detection of cyanide ion, Sensor Actuat. B Chem. 279 (2019) 189–196.
[38] H.E. Ok, F. Tian, E. Hong, O. Paek, S.H. Kim, D. Kim, H. Chun, Harmonized collaborative validation of aflatoxins and sterigmatocystin in white rice and sorghum by liquid chromatography coupled to tandem mass spectrometry, Toxins 8 (12) (2016) 371.
[39] R. Zekavati, S. Safi, S.J. Hashemi, T. Rahmani-Cherati, M. Tabatabaei, A. Mohsenifar, M. Bayat, Highly sensitive FRET-based fluorescence immunoassay for aflatoxin B1 using cadmium telluride quantum dots, Microchim. Acta. 180 (13–14) (2013) 1217–1223.
[40] J.M. Liu, X.Y. Yuan, H.L. Liu, D. Cheng, S. Wang, Fabrication of an activatable hybrid persistent luminescence nanoprobe for background-free bioimaging-guided investigation of food-borne aflatoxin *in vivo*, RCS Adv. 8 (50) (2018) 28414–28420.
[41] Y.-J. Li, X.-P. Yan, Synthesis of functionalized triple-doped zinc gallogermanate nanoparticles with superlong near-infrared persistent luminescence for long-term orally administrated bioimaging, Nanoscale 8 (2016) 14965–14970.
[42] X. Zhang, N.Y. Xu, Q. Ruan, D.Q. Lu, Y.H. Yang, R. Hu, A label-free and sensitive photoluminescence sensing platform based on long persistent luminescence nanoparticles for the determination of antibiotics and 2,4,6-trinitrophenol, RSC Adv. 11 (8) (2018) 5714–5720.
[43] D. Maurel, L. Comps-Agrar, C. Brock, M.-L. Rives, E. Bourrier, M.A. Ayoub, H. Bazin, N. Tinel, T. Durroux, L. Prézeau, E. Trinquet, J.-P. Pin, Cell-surface protein-protein interaction analysis with time-resolved FRET and snap-tag technologies: application to GPCR oligomerization, Nat. Methods 5 (6) (2008) 561–567.
[44] S.H. Kim, J.R. Gunther, J.A. Katzenellenbogen, Monitoring a coordinated exchange process in a four-component biological interaction system: development of a time-resolved terbium-based one-donor/three-acceptor multicolor FRET system, J. Am. Chem. Soc. 132 (13) (2010) 4685–4692.
[45] Y.S. Liu, S.Y. Zhou, D.T. Tu, Z. Chen, M.D. Huang, H.M. Zhu, E. Ma, X.Y. Chen, Amine-functionalized lanthanide-doped zirconia nanoparticles: optical spectroscopy, time-resolved fluorescence resonance energy transfer biodetection, and targeted imaging, J. Am. Chem. Soc. 134 (36) (2012) 15083–15090.
[46] L. Zang, J.P. Lei, J.T. Liu, F.J. Ma, H.X. Ju, Persistent luminescence nanoprobe for biosensing and lifetime imaging of cell apoptosis via time-resolved fluorescence resonance energy transfer, Biomaterials 67 (2015) 323–334.
[47] J. Li, C. Yang, W.-L. Wang, X.-P. Yan, Functionalized gold and persistent luminescence nanoparticle-based ratiometric absorption and TR-FRET nanoplatform for high-throughput sequential detection of L-cysteine and insulin, Nanoscale 10 (2018) 14931–14937.
[48] G.A. Posthuma-Trumpie, J. Korf, A.V. Amerongen, Lateral flow (immuno)assay: its strengths, weaknesses, opportunities and threats. A literature survey, Anal. Bioanal. Chem. 393 (2) (2009) 569–582.
[49] L.G. Lee, E.S. Nordman, M.D. Johnson, M.F. Oldham, A low-cost, high-performance system for fluorescence lateral flow assays, Biosens. Bioelectron. 3 (4) (2013) 360–373.
[50] A.S. Paterson, B. Raja, G. Garvey, A. Kolhatkar, A.E.V. Hagström, K. Kourentzi, T. Randall Lee, R.C. Willson, Persistent luminescence strontium aluminate nanoparticles as reporters in lateral flow assays, Anal. Chem. 86 (19) (2014) 9481–9488.