Review

Recent advances in design of lanthanide-containing NIR-II luminescent nanoprobes

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SUMMARY

Luminescent biosensing in the second near-infrared window (NIR-II, 1000–1700 nm) region, which has weak tissue scattering and low autofluorescence, draws extensive attention owing to its deep tissue penetration, good spatial resolution and high signal-to-background ratio. As a new generation of NIR-II probes, lanthanide (Ln3+)–containing nanoprobes exhibit several superior properties. With the rapid development of Ln3+-containing NIR-II nanoprobes, many significant advances have been accomplished in their optical properties tuning and surface functional modification for further bioapplications. Rather than being exhaustive, this review aims to survey the recent advances in the design strategies of inorganic Ln3+-containing NIR-II luminescent nanoprobes by highlighting their optical performance optimization and surface modification approaches. Moreover, challenges and opportunities for this kind of novel NIR-II nanoprobes are envisioned.

INTRODUCTION

In the second near-infrared (NIR-II, 1000–1700 nm) window, the effects of scattering and autofluorescence that come from endogenous fluorophores in tissues are minimized with the increasing wavelengths (Fan and Zhang, 2019; He et al., 2019; Li et al., 2020c; Naczynski et al., 2013; Wang et al., 2019). Compared with NIR-I imaging, NIR-II imaging can afford higher resolution with deeper penetration depth and lower background noise in biological tissues, which shows more potential for clinical translation (Diao et al., 2015; Kong et al., 2016; Wang et al., 2018d; Hu et al., 2020a, 2020b). With the development of noninvasive NIR-II imaging technique, the exploitation of efficient NIR-II luminescent probes has become an urgent task (He et al., 2018; Zhong and Dai, 2020). So far, the most developed NIR-II probes mainly fall into five categories: single-walled carbon nanotubes (SWCNTs) (Kodach et al., 2010; Welsher et al., 2009), quantum dots (QDs) (Dong et al., 2013; Xu et al., 2016), conjugated polymers (Hong et al., 2014; Reineck and Gibson, 2017), organic dyes (Antaris et al., 2016; Semonin et al., 2010; Thimsen et al., 2017), and lanthanide (Ln3+)–containing probes (Dai et al., 2017; Stouwdam and van Veggel, 2002; Xu et al., 2019; Heffern et al., 2014; Peng et al., 2020; Ning et al., 2019; Jin et al., 2020; Hu et al., 2017). Among them, SWCNTs usually exhibit broadband emission (>300 nm) and low photoluminescence (PL) quantum yields (QYs) (0.1–0.4%). QDs mostly face the problem of high toxicity (Wang and Zhang, 2014). As for conjugated polymers and organic dyes, they both display low solubility in aqueous solutions and suffer from photobleaching (Escobedo et al., 2010; Shen et al., 2020). All these drawbacks limit their practical bioapplications. In comparison with the aforementioned NIR-II probes, Ln3+-containing NIR-II luminescent nanoprobes are particularly intriguing because of their unique electronic structures and optical properties. Ln3+ ions have the electron configuration \(4f^n5s^25p^6\) \((n = 0–14)\). Specifically, the rich energy levels of Ln3+ endow their emissions covering from UV, visible to NIR. Among Ln3+ ions, several ions like Yb3+, Tm3+, Er3+, Ho3+, Dy3+, Sm3+, Nd3+, and Pr3+ were reported to produce NIR-II light (Naczynski et al., 2013; Yu et al., 2019). The inner 4f-4f transitions of these Ln3+ are insensitive to outer environment due to the effective shielding of 4f orbitals by the filled 5s and 5p orbitals, which results in sharp and tunable emissions with high photostability. As a new generation of NIR-II probes, Ln3+-containing nanoparticles (NPs) show great potential for multiplexed sensing, time-gated detection, and high-resolution imaging (Naczynski et al., 2014; Tan et al., 2020; Yu et al., 2008; Zhang et al., 2015; Wang et al., 2017a; Huang et al., 2015).

To date, significant efforts have been made to design highly efficient Ln3+-containing NIR-II luminescent nanoprobes (Liu et al., 2011; Swabeck et al., 2018; Xiao et al., 2013; Yu et al., 2008; Zhou et al., 2013). It
should be noted that most of the recently published reviews mainly emphasized on the chemistry and potential applications of Ln³⁺-containing NIR-II nanoprobes in bioimaging, biodetection, and disease theranostics (Yu et al., 2020; Li et al., 2020b; Wang and Zhang, 2016). Up to now, few reviews focused on their fundamental electronic structures and optical design, which should be renewed since more progress or new understandings have been gained in the past few years. Therefore, in this review, we provide a comprehensive survey of the latest advances toward the design of inorganic Ln³⁺-containing NIR-II nanoprobes, which covers from their fundamental electronic structures to novel design strategies, highlighting the optical performance optimization and surface modification approaches. This review will be organized as shown in Figure 1. Firstly, we start by the localized electronic structures of Ln³⁺-containing NIR-II nanoprobes. Then, the optical properties tuning of NIR-II nanoprobes will be reviewed, with emphasis on excitation/emission manipulation, PL lifetime manipulation, and PL intensity improvement. Furthermore, a variety of surface modification strategies like inorganic shell coating, organic polymer modification, and biofunctional agent conjugation will be briefly discussed. Finally, emerging trends and further efforts are proposed.

**LOCALIZED ELECTRONIC STRUCTURES**

Inorganic Ln³⁺-containing NPs are typically composed of Ln³⁺ emitters and a suitable inorganic host, which possesses good photo-chemical stability and high optical damage threshold. The intricate optical properties of trivalent Ln³⁺ originate from their 4fⁿ inner shell configurations, which have very localized states and can be conventionally described with crystal-field (CF) theory. Located in a dielectric crystal, the energy levels of Ln³⁺ ions split under the influence of the electric field produced by the crystalline environment. A small difference of the localized electronic structures may result in significant change in the electronic energy levels and excited-state dynamics of the doped Ln³⁺ ions. In this section, the site symmetry of Ln³⁺ ions and the microstructure manipulation of Ln³⁺-containing NIR-II nanoprobes are surveyed, which are essentially important to design novel Ln³⁺-containing NIR-II luminescent nanoprobes.

**Site symmetry of lanthanide ions**

The optical properties of Ln³⁺ strongly depend on the local site symmetry and CF surroundings around Ln³⁺. The inorganic NPs generally suffer from structure distortion and surface defects after the introduction of Ln³⁺ ions into their lattices, which may lead to the multiple sites of Ln³⁺ with diverse CF surroundings. Accordingly, the site symmetries of Ln³⁺ ions in the inorganic NPs can be verified by means of high-resolution site-selective or time-resolved PL spectroscopy.

As a typical example, our group employed Eu³⁺ as a spectroscopic probe to unveil the local site symmetry of NIR-II LiLuF₄:Nd³⁺ NPs through high-resolution PL spectroscopy (Huang et al., 2019). The detailed assignment of the CF transition lines of Eu³⁺ was achieved through 10 K PL spectra of LiLuF₄:5 mol% Eu³⁺ NPs to avoid thermal broadening of spectral lines at room temperature. As a result, total numbers of 0, 2, 3, 4, and 4 CF transition lines of Eu³⁺ from D2 to F7, F7, F7, F7, and F7 can be discerned in LiLuF₄.
NPs. Subsequently, the Eu$^{3+}$ ions were verified to occupy a single spectroscopic site through site-selective excitation and emission spectra. According to the branching rules and the transition selection rules of the 32 point groups, the spectroscopic site symmetry of Eu$^{3+}$ in LiLuF$_4$ NPs was determined to be S$^4$, which agreed well with the crystallographic site symmetry of Lu$^{3+}$ in LiLuF$_4$. Invoking the closeness in ion radii and chemical properties of Ln$^{3+}$ ions, it is suggested that Nd$^{3+}$ ions are prone to occupy a single spectroscopic site of S$^4$ symmetry in LiLuF$_4$ NPs at low doping levels (<5 mol%). Furthermore, a total number of 36 CF transition lines of Nd$^{3+}$ in the NIR region and the corresponding CF levels were unequivocally assigned with the help of temperature-dependent PL spectroscopy (Figure 2). By monitoring the Nd$^{3+}$ emission at 1053.2 nm, the excitation peaks at 861.4 and 865.9 nm were clearly observed in the PL excitation spectrum of Nd$^{3+}$ in LiLuF$_4$ NPs, which were ascribed to the CF transitions of Nd$^{3+}$ from the 4I$^9/2$ ground state to the upper (R$^2$) and lower (R$^1$) Stark sublevels of 4F$^3/2$, respectively. This implies that the CF levels of Nd$^{3+}$ are doubly degenerate in LiLuF$_4$ NPs. Upon selective excitation with 808-nm diode laser and 791.3-nm xenon lamp, respectively, the identical emission patterns unambiguously confirmed that Nd$^{3+}$ ions in the LiLuF$_4$ NPs occupied a single spectroscopic site. The total numbers of 10, 12, and 14 CF transition lines of Nd$^{3+}$ from 4F$^3/2$ to 4I$^9/2$, 4I$^{11/2}$, and 4I$^{13/2}$ agreed well with the theoretically predicted numbers for Nd$^{3+}$ in LiLuF$_4$.

Figure 2. Assignment of the CF transition lines of Nd$^{3+}$ in LiLuF$_4$ NPs through high-resolution PL spectroscopy
(A) 10 K PL excitation spectrum of LiLuF$_4$:2 mol%Nd$^{3+}$ NPs by monitoring the Nd$^{3+}$ emission at 1053.2 nm. Inset shows two CF transition lines from the 4I$^9/2$ ground state to the upper and lower Stark sublevels of 4F$^3/2$.
(B) 10 K PL emission spectrum of LiLuF$_4$:2 mol%Nd$^{3+}$ NPs upon excitation at 791.3 nm.
(C) Temperature-dependent PL emission spectra (10–300 K) for the 4F$^3/2$ → 4I$^J$ (J = 9/2, 11/2, and 13/2) CF transitions of Nd$^{3+}$ in LiLuF$_4$ NPs upon 808-nm diode laser excitation at a power density of 1 W cm$^{-2}$. The spectra were normalized at the maximum intensities at 880.4, 1053.1, and 1325.1 nm for the emissions from 4F$^3/2$ to 4I$^9/2$, 4I$^{11/2}$, and 4I$^{13/2}$, respectively. The dash lines denote the CF transitions from the R$^1$ (black) and R$^2$ (red) Stark sublevels of 4F$^3/2$ to those of 4I$^J$.
(D) CF energy levels of the 4F$^3/2$ and 4I$^J$ multiplets of Nd$^{3+}$ in LiLuF$_4$ NPs, showing all CF transitions observed in (C). Reproduced with permission from Huang et al. (Huang et al., 2019). Copyright 2019, Wiley-VCH.
with doubly degenerate CF levels. Based on the well-resolved CF transition lines from the thermally coupled Stark sublevels of $^4F_{3/2}$ of Nd$^{3+}$, the application of LiLuF$_4$:Nd$^{3+}$ NPs as sensitive NIR-to-NIR luminous nanoprobes for ratiometric detection of cryogenic temperature was subsequently illustrated.

**Microstructure manipulation**

As is well known, the selection of host lattice with specific symmetry will strongly influence the optical properties of Ln$^{3+}$ dopants (Tu et al., 2013). Besides, the cation incorporation strategy was also demonstrated to effectively manipulate the microstructure of Ln$^{3+}$-containing NIR-II luminescent NPs to improve their optical performance.

Typically, Y$^{3+}$ ions were co-doped into CaF$_2$:Nd$^{3+}$ NPs to regulate the local site symmetry for efficient NIR-II emitting of Nd$^{3+}$ (Yu et al., 2018; Quintanilla et al., 2018). The CaF$_2$ lattice comprises fluorine atoms at the corners of cubes and an alternate calcium atom. Nd$^{3+}$ ions were incorporated into the lattice to substitute Ca$^{2+}$ ions (Figure 3A). As a result of charge compensation, a F$^{-}$/Ca$^{2+}$ interstitial site was produced (Figure 3B). Upon increasing Nd$^{3+}$ concentration, Nd$^{3+}$-F$^{-}$ emitting pairs were created and may form clustering at even higher concentrations (Figure 3C). The formation of clustering reduced the distance of neighboring Nd$^{3+}$ ions, facilitating the unwanted nonradiative transitions. It was revealed that the clustering occurred at rather low Nd$^{3+}$ concentrations (~1 mol%) in CaF$_2$. With the addition of Y$^{3+}$ ions into the CaF$_2$ host, the structures of Nd$^{3+}$-Nd$^{3+}$ clusters were broken and the nonradiative relaxation paths can be hindered. The NIR-II QY of CaF$_2$:Nd$^{3+}$, Y$^{3+}$ NPs was measured to be 9.30%, which was ~3 times higher than that of CaF$_2$:Nd$^{3+}$ NPs. In a parallel study, transition metal ions like Zn$^{2+}$ ions were incorporated into NaYbF$_4$:Er$^{3+}$, Ce$^{3+}$@NaYF$_4$ counterparts to further improve the NIR-II PLQY through the doping-caused distortion of local symmetry around Er$^{3+}$ ions (Zhong et al., 2019).

**OPTICAL PROPERTY DESIGNING**

Benefiting from the peculiar electronic structures of Ln$^{3+}$, a variety of inorganic Ln$^{3+}$-containing NIR-II luminescent nanoprobes have been developed (Table 1). To engineer their optical properties for various bio-applications, many efforts have been devoted through tuning the host-dopant combination, the dopant concentration, and the morphology of particles. In this section, we will highlight the strategies of optical property design for these Ln$^{3+}$-containing NIR-II nanoprobes.
Excitation manipulation

Currently, the most commonly used excitation wavelength for Ln\(^{3+}\)-containing NIR-II nanoprobes is 980 nm, which matches well with the absorption of Yb\(^{3+}\) (2\(^{F_{7/2}}\) → 2\(^{F_{5/2}}\)) (Zhang et al., 2018; Zheng et al., 2015). Upon excitation with a commercial 980-nm diode laser, Yb\(^{3+}\) can absorb and transfer the energy to activators such as Er\(^{3+}\), Tm\(^{3+}\), and Nd\(^{3+}\). However, the narrow band absorption and low absorption coefficient of Yb\(^{3+}\) limit their further applications. Additionally, 980-nm laser may cause serious tissue overheating problem owing to the significant absorption by water molecules. These concerns greatly motivate the excitation manipulation of these Ln\(^{3+}\)-containing NIR-II nanoprobes, with the aim of overcoming the restrictions of 980-nm excitation.

Generally, NIR-II luminescence of Ln\(^{3+}\) ions can be achieved through direct excitation or introducing efficient sensitizers (Cheng et al., 2018; Zhang et al., 2020a). Compared with direct excitation, the sensitizers which have broader absorption bands and larger absorption cross-sections can promote the activators to higher excited states through energy transfer (ET) process and then lead to efficient NIR-II emitting. Therefore, suitable sensitizers including organic dyes, QDs, and Ln\(^{3+}\) ions were developed to manipulate the excitation.

As antenna, organic dyes with large absorption cross sections were widely selected to broaden the excitation of Ln\(^{3+}\)-containing luminescent NPs. In 2012, Zou et al. (2012) first reported the ET process from the NIR dye IR-806 to NaYF\(_4\):Yb\(^{3+}\),Er\(^{3+}\) NPs. Benefiting from the dye-sensitized process and increased absorption cross-section, the excitation spectral response was expanded to a broad range of 720–1000 nm. Inspired by this work, a series of organic dyes were adopted to sensitize Ln\(^{3+}\) NIR luminescence, including indocyanine green (Wang et al., 2018a), MY-1057 (Zhao et al., 2020), and IR-1061 (Hazra et al., 2018).

Besides dye sensitization, QDs were also explored as light harvesting materials. CdSe (Martin-Rodriguez et al., 2013), InP (Klik et al., 2002; Swabec et al., 2018), and CsPbX\(_3\) QDs were reported to sensitize the NIR emissions of Ln\(^{3+}\). Among them, CsPbX\(_3\) perovskite QDs have drawn most attention because of their broadband absorption and excellent optical properties. Pan et al. (2017) demonstrated that NIR emission was obtained from Yb\(^{3+}\)-doped CsPbCl\(_3\) QDs upon the excitation of 365-nm light. The sensitization of CsPbCl\(_3\) host with large absorption coefficient endowed Yb\(^{3+}\) excitation at a broad ultraviolet component.

| Activator | Nanoprobe | Ex/Em wavelength (nm) | Energy level transition | PLQY (\%) | Reference |
|-----------|-----------|-----------------------|-------------------------|-----------|-----------|
| Nd\(^{3+}\) | NaGdF\(_4\):Yb\(^{3+}\), Nd\(^{3+}\), Tm\(^{3+}\) | 808/1000 | \(^{4}F_{3/2} \rightarrow ^{4}I_{11/2}\) | 11 | Tan et al., 2018 |
| NaNdF\(_4\): Mn\(^{2+}\) | 808/1058, 1320 | \(^{4}F_{3/2} \rightarrow ^{4}I_{11/2}\), \(^{4}F_{3/2} \rightarrow ^{4}I_{13/2}\) | 10 | (Wang et al., 2018c) |
| CaF\(_2\): Y\(^{3+}\), Nd\(^{3+}\) | 808/1058, 1328 | \(^{4}F_{3/2} \rightarrow ^{4}I_{11/2}\), \(^{4}F_{3/2} \rightarrow ^{4}I_{13/2}\) | 9.3 | Lei et al., 2018 |
| NaYF\(_4\):Nd\(^{3+}\)@NaYF\(_4\) | 808/1064, 1345 | \(^{4}F_{3/2} \rightarrow ^{4}I_{11/2}\), \(^{4}F_{3/2} \rightarrow ^{4}I_{13/2}\) | 7.9, 4.1 | Li et al., 2019a |
| CaS:Ce\(^{3+}\), Nd\(^{3+}\) | 450/1070 | \(^{4}I_{3/2} \rightarrow ^{4}I_{11/2}\) | 7.7 | Zhang et al., 2019b |
| Er\(^{3+}\) | CaS:Ce\(^{3+}\), Er\(^{3+}\) | 450/1540 | \(^{4}I_{13/2} \rightarrow ^{4}I_{15/2}\) | 9.3 | Zhang et al., 2019b |
| NaYF\(_4\):Gd\(^{3+}\), Yb\(^{3+}\), Er\(^{3+}\) | 980/1520 | \(^{4}I_{13/2} \rightarrow ^{4}I_{15/2}\) | 0.994 | Xue et al., 2018 |
| NaCeF\(_3\):Er\(^{3+}\), Yb\(^{3+}\) | 980/1530 | \(^{4}I_{13/2} \rightarrow ^{4}I_{15/2}\) | 32.8 | Lei et al., 2018 |
| NaYF\(_4\):Er\(^{3+}\)@ICG | 808/1520 | \(^{4}I_{13/2} \rightarrow ^{4}I_{15/2}\) | 3.1 | Wang et al., 2018a |
| NaErF\(_4\):Yb\(^{3+}\)@NaLuF\(_4\) | 808/1525 | \(^{4}I_{13/2} \rightarrow ^{4}I_{15/2}\) | 11 | Wang et al., 2018c |
| Ho\(^{3+}\) | Ba\(_5\)In\(_2\)O\(_8\): Yb\(^{3+}\), Ho\(^{3+}\) | 980/1192 | \(^{3}I_{6} \rightarrow ^{3}I_{8}\) | - | Wang et al., 2018e |
| NaErF\(_4\):Ho\(^{3+}\)@NaYF\(_4\) | 1530/1180 | \(^{3}I_{6} \rightarrow ^{3}I_{8}\) | - | Liu et al., 2018 |
| NaYF\(_4\):Er\(^{3+}\), Ho\(^{3+}\), Yb\(^{3+}\) | 1532/1172 | \(^{3}I_{6} \rightarrow ^{3}I_{8}\) | - | Cheng et al., 2018 |
| NaYF\(_4\):Yb\(^{3+}\), Ho\(^{3+}\)@NaYF\(_4\) | 980/1185 | \(^{3}I_{6} \rightarrow ^{3}I_{8}\) | - | Naczynski et al., 2013 |
| Tm\(^{3+}\) | NaYF\(_4\):Yb\(^{3+}\), Tm\(^{3+}\)@NaYF\(_4\) | 980/1475 | \(^{3}H_{4} \rightarrow ^{3}F_{4}\) | - | Naczynski et al., 2013 |
| Pr\(^{3+}\) | NaYF\(_4\):Yb\(^{3+}\), Pr\(^{3+}\)@NaYF\(_4\) | 980/1310 | \(^{3}G_{4} \rightarrow ^{3}H_{5}\) | - | Naczynski et al., 2013 |
from 270 to 420 nm. Subsequently, Zhu et al. (2020) also reported CsPbCl₃:Er³⁺,Yb³⁺ QDs with NIR-II emission of Er³⁺ ions upon 365-nm excitation.

For Ln³⁺ sensitization, a new class of NIR-II luminescent nanoprobes of CaS: Ce³⁺, Er³⁺, and Nd³⁺ in CaS NPs was recently reported by our group (Zhang et al., 2019b). The NIR-II luminescence of Er³⁺ and Nd³⁺ was realized through sensitization of Ce³⁺ (Figures 4A and 4B), which can be effectively excited using a low-cost blue light-emitting diode chip. With the rapid development of NIR optical imaging, there is an increased demand for the NIR-II luminescent probes with the excitation light located in the NIR region. In such NIR region, the excitation light with low water absorption and tissue overheating is more favorable for in vivo imaging. To address this concern, attempts were made to enrich excitation wavelengths by employing NIR-excitable Ln³⁺ ions as sensitizers, including Nd³⁺, Er³⁺, and Tm³⁺. Nd³⁺ has multiple absorption positions and relatively large cross-section compared to Yb³⁺. Utilizing Nd³⁺ as a sensitizer, the excitation wavelength can be shifted to 808 nm (Wang et al., 2013). Water absorption is much lower with an absorption

Figure 4. Excitation manipulation of Ln³⁺-containing NIR-II luminescent nanoprobes
(A) Schematic illustration of the ET from Ce³⁺ to Er³⁺ and Nd³⁺ in CaS NPs.
(B) Simplified energy levels of Ce³⁺, Er³⁺, and Nd³⁺ in CaS NPs, showing the proposed ET processes for the population of 4I13/2 of Er³⁺ and 5F7/2 of Nd³⁺ through sensitization by Ce³⁺. The dashed, dotted and full arrows represent the ET, nonradiative relaxation and radiative transition processes, respectively.
(C) Schematic design of the as-synthesized NaYF₄:Tm³⁺@NaYF₄ and NaYF₄:Tm³⁺, Er³⁺@NaYF₄ NPs excited by a 1208-nm laser (10 W cm⁻²).
(D) Simplified ET pathway from Tm³⁺ to Er³⁺.
(E) X-IR system used to image Ln³⁺-doped NPs consists of a highly sensitive NIR-II detector and X-ray irradiator.
(F) Distinct focal luminescence was visualized away from the injection site near the animal’s axillary and brachial lymph nodes.

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coefficient of 0.02 cm\(^{-1}\) at 808 nm, in contrast to 0.48 cm\(^{-1}\) at 980 nm. Accordingly, the laser-induced tissue heating effect was minimized. It should be noted that Yb\(^{3+}\) are generally doped into Nd\(^{3+}\)-sensitized NPs as bridging ions to guarantee the efficient sensitization. Based on this concept, a series of NIR-II Nd\(^{3+}\)/Yb\(^{3+}\)/Ln\(^{3+}\) doped NPs, such as NaGdF\(_4\):Yb\(^{3+}\),Nd\(^{3+}\),Tm\(^{3+}\) (Tan et al., 2018), NaGdF\(_4\):Nd\(^{3+}\)@NaGdF\(_4\):Tm\(^{3+}\), Yb\(^{3+}\) (Wang et al., 2014), and NaGdF\(_4\):Na(Gd,Yb)F\(_4\):Er\(^{3+}\)@NaYF\(_4\):Yb\(^{3+}\)@NaNdF\(_4\):Yb\(^{3+}\) (He et al., 2015), were further proposed.

Besides Nd\(^{3+}\)-sensitized NPs, a series of Er\(^{3+}\)-sensitized NPs have also been reported. Wang et al. (2018d) described a class of NIR-II luminescent nanoprobes of NaErF\(_4\):Yb\(^{3+}\)@NaLuF\(_4\), which can be efficiently excited at ~800 nm, benefiting from the self-sensitization process of Er\(^{3+}\) ions. To open new possible avenues for deep tissue imaging, the decent absorption peak of Er\(^{3+}\) at ~1530 nm is adopted to expand the excitation wavelength in the NIR-II region. As a typical example, the NaErF\(_4\):Ln\(^{3+}\)@NaYF\(_4\) (Ln\(^{3+}\) = Ho\(^{3+}\) or Nd\(^{3+}\)) NPs were demonstrated to produce 1525 nm NIR-II luminescence from Tm\(^{3+}\) sensitizer to Er\(^{3+}\) emitter via the efficient ET process (Figures 4C and 4D) (Zhang et al., 2019a). Upon 808-nm excitation, Ho\(^{3+}\) emitter showed the NIR-II emission at 1180 nm in NaYF\(_4\):Tm\(^{3+}\), Ho\(^{3+}\)@NaYF\(_4\) NPs.

Besides NIR light source, X-ray has become a promising new excitation source to produce NIR-II emission (Figures 4E and 4F) (Naczynski et al., 2015). The X-ray excitation allows probes to be excited at essentially any depth in the human body, eliminates the background signal generated by tissue autofluorescence, and simplifies image reconstruction for optical tomography. For instance, NaYF\(_4\):Yb\(^{3+}\), Er\(^{3+}\) NPs were demonstrated to generate a distinct NIR-II emission peak centered at ~1530 nm after X-ray irradiation and show their potential for deep tissue imaging applications. However, few X-ray excitable Ln\(^{3+}\)-containing NIR-II nanoprobes have been reported. Much work is still needed to exploit X-ray excitable Ln\(^{3+}\)-containing nanoprobes with bright NIR-II luminescence.

### Emission manipulation

Benefiting from the rich energy levels, abundant wavelengths of Ln\(^{3+}\) in the NIR-II region can be achieved. In addition, Ln\(^{3+}\) ions typically exhibit much narrower emission band widths than that of QDs and organic dyes, which can reduce signal interference in both in vivo bioimaging and in vitro biodetection. As such, many efforts have been devoted to manipulating NIR-II emission to meet the requirements for the proposed applications.

For example, Nd\(^{3+}\)-doped NaGdF\(_4\) NPs showed three PL bands peaking at 900, 1050, and 1330 nm upon 740-nm excitation, which were assigned to the transitions from \(^{4}F_{3/2}\) to \(^{4}I_{J}\) (J = 9/2, 11/2, 13/2) (Chen et al., 2012). These NIR emissions within “optical transparency window” were exceptionally sharp, which made NaGdF\(_4\):Nd\(^{3+}\) NPs an ideal luminescent probe for high-contrast in vivo imaging. Besides Nd\(^{3+}\) ions, Pr\(^{3+}\) (\(^{4}I_{11/2} \rightarrow ^{4}I_{9/2}\)), Ho\(^{3+}\) (\(^{3}I_{6} \rightarrow ^{3}I_{5}\)), Er\(^{3+}\) (\(^{4}I_{13/2} \rightarrow ^{4}I_{15/2}\)), and Tm\(^{3+}\) (\(^{3}H_{4} \rightarrow ^{3}F_{4}\)) also show great potential for constituting NIR-II luminescent materials because their emissions are located in the spectral region of 1000–1700 nm (Figures 5A–5C) (Naczynski et al., 2013). By utilizing these Ln\(^{3+}\) ions, NIR-II luminescent probes with multicolor emissions were designed for applications in multispectral imaging and multiplexed biodetection.

Ratiometric optical nanoprobes are favorable for providing an increased signal-to-background ratio and more reliable results in bioimaging and biosensing. With the development of these ratiometric nanoprobes, several Ln\(^{3+}\)-containing NIR-II luminescent materials with two or multiple non-overlapped emissions were designed. For example, NaErF\(_4\):Ho\(^{3+}\)@NaYF\(_4\) NPs emitted efficient emission at 1180 nm upon 1530-nm excitation (Figures 5D–5F) (Liu et al., 2018). Acting as both sensitizer and emitter, Er\(^{3+}\) showed emissions peaked at 650 nm (\(^{4}F_{9/2} \rightarrow ^{4}I_{15/2}\)) and 980 nm (\(^{4}I_{11/2} \rightarrow ^{4}I_{15/2}\)), respectively. Meanwhile, the emission peaked at 1180 nm was also detected due to the ET process from Er\(^{3+}\) to Ho\(^{3+}\). By taking advantage of the NIR emissions of Er\(^{3+}\) and Ho\(^{3+}\), novel ratiometric luminescent (I\(_{980}/I_{1180}\)) nanoprobes were designed for in vivo inflammation dynamic detection.
Photoluminescence lifetime manipulation

The PL lifetime is an important parameter for Ln$^{3+}$-containing NPs. Recently, the time-domain NIR-II nanoprobes show enormous potential in bioimaging because PL lifetime can avoid inhomogeneous signal attenuation in biological tissues. As such, Ln$^{3+}$-doped NIR-II NPs with engineered PL lifetime were developed through controlling their structure and composition.

The nonradiative relaxation caused by surface defects may significantly affect the PL lifetime of Ln$^{3+}$-containing NPs. By virtue of efficient surface passivation treatment, time-domain luminescent NPs were obtained by coating an inert shell on the Ln$^{3+}$-containing NPs. For instance, the PL lifetime of the core-shell $\alpha$-NaYbF$_4$@CaF$_2$ NPs with NIR emission can be tuned from 33 μs to 2.18 ms by controlling the thickness of CaF$_2$ shells (Gu et al., 2019). It was determined that the optimal thickness of the CaF$_2$ inert shell was 2.6 nm, which was sufficient to overcome the surface-quenching-induced concentration quenching. Correspondingly, the PL lifetime was prolonged close to the radiative lifetime of Yb$^{3+}$.

In 2018, Fan et al. (2018) proposed a systematic approach to tune the PL lifetime by controlling the energy relay in a core/multi-shell structure (Figures 6A–6C), which consisted of four components, including the inert core (NaGdF$_4$), the activation layer (NaGdF$_4$:Yb$^{3+}$, Er$^{3+}$), the energy relay layer (NaYF$_4$:Yb$^{3+}$), and the outer absorption layer (NaNdF$_4$:Yb$^{3+}$). These core/multi-shell NPs absorbed 808-nm photons to generate emission centered at 1525 nm through efficient Nd$^{3+}$/Yb$^{3+}$/Er$^{3+}$ ET process. The lifetime-engineering was accomplished in two directions. One was prolonging the average process from absorption to emission through increasing the thickness of the energy relay layer, leading to a longer PL lifetime. The other was accelerating the conversion of stored energy into PL emission via increasing the Er$^{3+}$ concentration, which shortened the PL lifetime. As a result, the PL lifetime of Er$^{3+}$ at 1525 nm can be tuned spanning three orders of magnitude. Based on these NPs, more than 10 distinct lifetime identities were clearly distinguished using a TR imaging system. Likewise, tunable lifetimes were achieved for other NIR-II Ln$^{3+}$ ions, including Ho$^{3+}$ with emission at 1155 nm, Pr$^{3+}$ with emission at 1289 nm, Tm$^{3+}$ with emission at 1475 nm, and Nd$^{3+}$ with emission at 1060 nm.

Figure 5. Emission manipulation of Ln$^{3+}$-containing NIR-II luminescent nanoprobes

(A) Rare-earth nanoprobes consist of a NaYF$_4$:Yb$^{3+}$, Ln$^{3+}$ core (Ln$^{3+}$:Er$^{3+}$, Ho$^{3+}$, Tm$^{3+}$ or Pr$^{3+}$) surrounded by an undoped shell of NaYF$_4$.

(B) NIR-II emissions from different Ln$^{3+}$ emitters like Ho$^{3+}$, Pr$^{3+}$, Tm$^{3+}$, and Er$^{3+}$.

(C) 1185, 1310, 1475, and 1525 nm emissions of Ho$^{3+}$, Pr$^{3+}$, Tm$^{3+}$, and Er$^{3+}$-doped NPs are attributed to the $^5I_6 \rightarrow ^5I_8$, $^1G_4 \rightarrow ^3H_6$, $^3H_4 \rightarrow ^3F_4$, and $^1I_{15/2} \rightarrow ^3I_{15/2}$ transitions, respectively.

(D) Simplified energy levels of Er$^{3+}$, Ho$^{3+}$ in NaErF$_4$:Ho$^{3+}$@NaYF$_4$ NPs, showing the proposed ET process through sensitization of Er$^{3+}$.

(F) Emission spectra of the obtained NIR-II NPs.

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Photoluminescence lifetime manipulation

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Besides manipulating core-shell structures of the Ln\(^{3+}\)-doped NPs, the incorporation of NIR-II dye with Ln\(^{3+}\)-doped NPs may provide an efficient ET pathway to tune PL lifetime of Ln\(^{3+}\). Zhao et al. (2020) reported a Förster resonance energy transfer (FRET) nanoprobe for quantitative luminescence-lifetime biosensing by employing the NIR-II dye MY-1057 encapsulated \(\beta\)-NaYF\(_4@NaYF\(_4\):Nd\(^{3+}\) NPs (Figure 6D). In these nanoprobes, \(\beta\)-NaYF\(_4@NaYF\(_4\):Nd\(^{3+}\) NPs were utilized as FRET donor with emission at 1060 nm, while MY-1057 was used as energy acceptor. Because of the Ln\(^{3+}\)–cyanine FRET process, the PL lifetime of Nd\(^{3+}\) may be decreased from 305 to 75 ms with the addition of MY-1057. The structure of MY-1057 degraded in response to reactive nitrogen species, subsequently leading to the lifetime recovery.

**Photoluminescence intensity improvement**

Currently, the low PL intensity of Ln\(^{3+}\)-containing NIR-II NPs owing to the small absorption cross-section of Ln\(^{3+}\) has been the major bottleneck for their commercial bioapplications. To this regard, researchers tried their best to design efficient Ln\(^{3+}\)-containing NIR-II luminescent nanoprobes through spatial distribution of dopants, effective surface passivation, manipulating the ET pathways, and optimizing host matrix, etc.

Theoretically, high doping concentration of Ln\(^{3+}\) ions provides more emitters, which might favor the light absorption and emitting, however the high doping will unavoidably cause localized concentration quenching of sensitizers or activators. Therefore, overcoming concentration quenching at high dopant concentration has become an urgent task for improved PL intensity.

Generally, concentration quenching is attributed to deleterious cross-relaxation between dopant ions in close proximity. Through manipulating the spatial distribution of the doped Ln\(^{3+}\) ions, the NIR-II emission identity can be improved. For example, considering the short spatial distances between Tm\(^{3+}\) and Nd\(^{3+}\) ions may aggravate the quenching of the NIR-II emission from Nd\(^{3+}\) at a high local concentration. The
spatial isolation was carried out to shield the unwanted ET process between Tm$^{3+}$ and Nd$^{3+}$ ions (Figures 7A–7C) (Johnson et al., 2017). As a result, the core-shell NaGdF$_4$:$\text{Nd}^{3+}$@NaGdF$_4$:Tm$^{3+}$, Yb$^{3+}$ NPs were synthesized with the optimized NIR-to-NIR emission intensity, which was increased by at least a factor of 7 as compared with the NaGdF$_4$:Nd$^{3+}$,Tm$^{3+}$,Yb$^{3+}$ counterparts.

Besides cross-relaxation between Ln$^{3+}$ ions, the energy migration from Ln$^{3+}$ to the defects may also deteriorate the NIR-II emission of Ln$^{3+}$ ions. Therefore, the epitaxial growth of a shell is widely adopted to spatially isolate the core with surface defects. It was demonstrated that in NaYF$_4$:Er$^{3+}$ NPs, the major quenching process at high dopant concentrations predominantly originated from energy migration from Er$^{3+}$ to the surface rather than cross-relaxation between dopants (Johnson et al., 2017). After coating with an inert NaLuF$_4$ shell, the intense NIR-II emission of Er$^{3+}$ was achieved (Figures 7D–7F). In their work, the NIR-II luminescence peaked at 1525 nm, corresponding to the $^4I_{15/2} \rightarrow ^4I_{13/2}$ transition of Er$^{3+}$, was enhanced by $\sim$659 times relative to that of their parent core-only NPs.

Figure 7. PL intensity improvement of Ln$^{3+}$-containing NIR-II luminescent nanoprobes through core-shell structure design

(A) Energy level diagrams of Nd$^{3+}$, Tm$^{3+}$, and Yb$^{3+}$ ions in NaGdF$_4$:Nd$^{3+}$@NaGdF$_4$:Tm$^{3+}$, Yb$^{3+}$ NPs. (B and C) Illustration of (B) the spatial structure and (C) cross-section of the core-shell structure with spatial isolated doping. (D) Energy level diagram of Er$^{3+}$ in $\beta$-NaErF$_4$@NaLuF$_4$ NPs, showing the excitation (808 nm) and the emission (1550 nm) levels. (E) Emission spectra of NaErF$_4$@NaLuF$_4$ NPs with variable Er$^{3+}$ dopant concentrations in the core, showing emission between 1450 and 1650 nm upon 808-nm excitation. (F) NIR-II emission images from colloidal dispersion of NaErF$_4$@NaLuF$_4$ NPs with varying shell thicknesses. (H) Dependence of emission spectra of NaErF$_4$@NaLuF$_4$ NPs on the shell thickness varying from 0 to 4.8 nm. (I) NIR-II intensity integrated from 1400 to 1700 nm versus the shell thickness for NaErF$_4$@NaYF$_4$ NPs. All the emission spectra were acquired upon laser excitation at 808 nm with an output power density 0.66 W/cm$^2$. (A–C) reproduced with permission from Zhou et al. (Zhou et al., 2013). Copyright 2013, American Chemical Society. (D–F) reproduced with permission from Johnson et al. (Johnson et al., 2017). Copyright 2017, American Chemical Society. (G–I) reproduced with permission from Li et al. (Li et al., 2020a). Copyright 2020, American Chemical Society.
Inspired by this work, Li et al. (2020a) revealed the shell thickness effect on the NIR-II luminescence from the NaErF4@NaYF4 NPs through elaborately modulating the shell thickness (Figures 7G–7I). As the shell thickness increasing from 0.5 to 3 nm, the NIR-II luminescence intensity of Er 3+ was enhanced gradually and showed a steady value for shell thickness over 3 nm. Finally, the absolute PLQY of NaErF4@NaYF4 NPs with the shell thickness of 3 nm was determined to be 10.2 ± 0.8% upon 808-nm laser excitation with power density of 0.1 W/cm². Apart from the utilization of shells with similar lattice parameters of the core, silica shell coating was adopted to suppress the vibrational quenching caused by the O–H groups and improve the NIR-II emission. For example, the NIR-II emission intensity of NdF3 NPs was enhanced by 1.6 times after coating the SiO2 shell (Yu et al., 2008).

In addition to inorganic shells, organic dye molecules were also attached to the surface of Ln3+-containing NPs for efficient NIR-II emitting. Typically, indocyanine green, as the light-harvesting surface ligand, was employed to sensitize NaYF4:Er3+ NPs (Wang et al., 2018a). Likewise, the named dye HC-Ni, which can be activated by glutathione (GSH), was modified on the surface of NaYF4:Yb3+, Er3+@NaYF4:Nd3+ NPs via hydrophobic interaction (Li et al., 2020c). With the addition of GSH, the NIR-II emission intensity of dye-modified NPs was markedly increased due to the target-triggered dye-sensitization process.

Another efficient way to enhance NIR-II luminescence is manipulating the ET pathways through cation incorporation. Specifically, in the core-shell NaErF4:Yb3+@NaLuF4 NPs, the doped Yb3+ ions acting as energy trapping centers, can induce back ET to populate the 4I13/2 level of Er3+ (Wang et al., 2018d). As a result, NaErF4@NaLuF4 with 20 mol% Yb3+ generated efficient NIR-II luminescence at 1525 nm with optimized PLQY of ~11% (emission range: 900–1700 nm) upon 808-nm excitation. In addition, Ce3+ was doped into Er3+-based NPs to boost the NIR-II emission of Er3+. Zhong et al. (2017) reported a NIR-II luminescence nanoprobe of core-shell NaYbF4:Er3+, Ce3+@NaYF4 NPs (Figure 8). The nonradiative phonon-assisted cross-relaxation of 5I11/2 → 4I13/2 of Er3+ was facilitated by the Ce3+ dopants due to the small mismatch of energy level between Ce3+ and Er3+ ions, which enhanced the population of the 4I13/2 level of Er3+.
Correspondingly, an increased NIR-II luminescence was achieved. In the presence of Ce\(^{3+}\) ions, the NIR-II luminescence of Er\(^{3+}\) was found to be 9-fold higher than that without Ce\(^{3+}\) doping. However, the low concentration of Ce\(^{3+}\) with only 2 mol% limited the further improvement of NIR-II PLQY. To this regard, our group synthesized NaCeF\(_4\):Er\(^{3+}\), Y\(_{b}^{3+}\)@NaCeF\(_4\) NPs (Lei et al., 2018). Upon excitation at 980 nm, the Ce\(^{3+}\) in the host lattice significantly enhanced the NIR-II luminescence of Er\(^{3+}\) at 1530 nm with a maximum NIR-II QY of 32.8%, which is the highest among Er\(^{3+}\)-activated inorganic nanoprobes.

SURFACE FUNCTIONAL MODIFICATION

The as-prepared Ln\(^{3+}\)-containing NIR-II luminescent nanoprobes are usually capped with hydrophobic ligands, which thus limit their bioapplications where hydrophilicity is a prerequisite. As a consequence, one crucial issue for the bioapplications of the hydrophobic Ln\(^{3+}\)-containing NIR-II luminescent materials is the surface functional modification, in an effort to render them water-soluble and provide reactive groups for subsequent bioconjugation to various biomolecules. To this end, a variety of surface modification strategies like inorganic shell coating, organic polymer modification, and biofunctional agent conjugation have been developed over the past decade, as will be briefly overviewed in this section.

Inorganic shell coating

Inorganic shells are frequently used to minimize the PL quenching of emitters from the surface ligands and liquid media. Meanwhile, some inorganic materials also endow the Ln\(^{3+}\)-containing NIR-II luminescent nanoprobes with good hydrophilicity. Generally, the inorganic shells can be classified as amorphous inorganic shells and crystalline inorganic shells. The amorphous inorganic shells with large surface area and tunable pore sizes can serve as efficient carriers for drug delivery and release. As a typical kind of amorphous inorganic shells, silica attracted considerable attention for bioapplications owing to its controllable synthesis, facile modification, and excellent biocompatibility. For instance, the NaGdF\(_4\):Nd\(^{3+}\)@NaGdF\(_4\) NPs were coated by mesoporous SiO\(_2\) for delivering drugs (Wang et al., 2017b). Moreover, the silica shells can be functionalized with molecular, supramolecular or polymer moieties, which provides the nanoprobes with more exciting opportunities for multimodal biosensing. Specifically, photosensitizing molecules can be embedded into mesoporous SiO\(_2\) shell for NIR-II luminescent-based photodynamic therapy applications (Tang et al., 2011). In addition, complexes that have potential in biodetection and bioimaging can be covalently linked with the silica shell to impart the nanoprobes with new functional features. For example, Gd\(^{3+}\) complex can endow NaLuF\(_4\):Yb\(^{3+}\), Tm\(^{3+}\) NPs with T\(_1\)-enhanced magnetic resonance, which holds the promise for both NIR luminescence imaging and magnetic resonance imaging (Xia et al., 2012).

The crystalline inorganic shells are generally prepared through epitaxial growth method. They have desirable properties such as ideal optical transparency and high crystallizability. These intriguing properties make them useful for minimizing the surface-related quenching effect of NIR-II NPs and improve resistance to aqueous quenchers (e.g., -OH, -NH\(_2\)). However, most crystalline inorganic shells are mainly restricted by the poor biocompatibility and monotonous function. Hence, it is desired to exploit the crystalline inorganic shells with good water dispersibility and superior biocompatibility. Compared with the most used NaYF\(_4\), CaF\(_2\) shell is more biocompatible because it is an endogenous component in live systems. Therefore, CaF\(_2\) was reported as the epitaxial shell to preserve the efficient luminescence of \(\alpha\)-NaYbF\(_4\) (Gu et al., 2019), NaYF\(_4\):Yb\(^{3+}\), Tm\(^{3+}\) NPs (Shen et al., 2013), and NaLuF\(_4\):Yb\(^{3+}\), Ln\(^{3+}\) (Ln\(^{3+}\) = Er\(^{3+}\), Ho\(^{3+}\), Tm\(^{3+}\)) (Li et al., 2017) in biological media.

Recently, our group reported a novel strategy to confer Ln\(^{3+}\) with target recognition ability and customizable surface attributes, based on the good biocompatibility and unique surface chemistry of single-layer graphene oxide (GO) (Figure 9) (Song et al., 2019). GO coating endowed NaYF\(_4\):Yb\(^{3+}\), Er\(^{3+}\)@NaYF\(_4\) NPs with amphiphilicity and high specific surface areas, thereby enabling them to be well dispersed in diverse solvents and stably modified with various agents through non-covalent interactions. In this work, the GO-coated NPs were functionalized with DNA for intracellular tracking and microRNA visualization. Moreover, the protein can be armored on these GO coated NPs for tumor-targeted NIR-II imaging.

Organic polymer modification

Organic polymers are the most frequently used agents for surface engineering of Ln\(^{3+}\)-containing NIR-II nanoprobes. To ensure the stable binding between organic polymers and inorganic NPs, three well-known
strategies have been proposed (Figure 10): (1) surface ligand exchange; (2) surface ligand attraction; (3) layer-by-layer electrostatic assembly. Hitherto, a number of organic polymers have been developed for surface engineering of Ln$^{3+}$-containing NIR-II nanoprobes. Among them, polyethylene glycol (PEG) is the most widely adopted and has been approved by FDA for human oral, intravenous, and dermal pharmaceutical applications. PEG molecules can be transformed into amphiphatic molecules through organic synthesis, resulting in hydrophobic groups as well as hydrophilic groups. For instance, the hydrophobic groups can be diphosphate, distearoyl phosphoethanolamine (DSPE), poly(lactic-co-glycolic acid), etc., while the hydrophilic groups can be carboxyl (COOH), maleimide, amidogen (NH$_2$), etc (Li et al., 2013). Being amphiphilic, nontoxic, non-immunogenic and non-antigenic, PEG as modifying polymer can markedly improve the water solubility and biocompatibility of Ln$^{3+}$-containing NIR-II luminescent nanoprobes. The hydrophobic portion of amphiphilic PEG polymers usually interacts with the organic capping layer of NPs via hydrophobic attraction, while the hydrophilic portion faces outwards, interacting with the aqueous solvent and rendering the particle water soluble, which is called the “surface ligand attraction” strategy. Typically, the amphiphilic 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[carboxy(polyethyleneglycol)-2000] (DSPE-PEG2000-COOH) phospholipids were used to coat the multi-shell NaGdF$_4$@Na(Gd, Yb)F$_4$;Er$^{3+}$@NaYF$_4$;Yb$^{3+}$@NaNdF$_4$;Yb$^{3+}$ NPs for NIR-II in vivo bioimaging via the surface ligand attraction strategy (Wang et al., 2014). The NPs can be easily transferred from the organic phase to the aqueous phase and remained excellent monodisperse. Moreover, the rich and adjustable functional groups render PEGylation suitable for various applications. For example, folic acid (FA), whose receptor overexpressed in cancer cells, was coupled onto the surface of the PEGylation NPs through covalent conjugation (Li et al., 2019c). The obtained NPs/FA conjugate was demonstrated to be a tumor-targeted NIR-II probe for simultaneously visualizing both subcutaneous and intraperitoneal tumor xenografts in vivo.

A series of other organic polymers such as polyacrylic acid (PAA), polydopamine (PDA), and polyvinyl alcohol were also employed for the surface modification of Ln$^{3+}$-containing NIR-II luminescent NPs. Zhang et al. (2007) first reported the use of ligand exchange strategy to convert oleic acid capped NPs into hydrophilic NPs. In a typical ligand exchange procedure, the original capping ligand of oleic acid on the surface of NaLu$_2$O$_3$Gd$^{3+}$, Nd$^{3+}$ NPs can be replaced with PAA (Li et al., 2019a). These PAA-modified NaLuF$_4$:Gd$^{3+}$, Nd$^{3+}$ NPs were observed to accumulate in the reticuloendothelial system and excreted through the hepatic
pathway. In another work, Dai et al. (2017) found that the thicker PDA layer covered on the NaYF₄:Nd³⁺@NaLuF₄ may enhance photothermal conversion efficiency of the resulting nanocomposites. Subsequently, Li et al. (2019b) exhibited non-invasive angiography of vascular malformations/tumors using NaLnF₄@PDA nanoprobes in the brain/abdomen of mice.

**Biofunctional agent conjugation**

Although surface coating of Ln³⁺-containing NIR-II nanoprobes with inorganic shells or organic polymers has been demonstrated to improve their biocompatibility, the targeting efficiency is still unsatisfied because of the poor accumulation ability and insufficient retention time. Hence, the surface engineering with bioactive agents such as antibodies (You et al., 2018), DNA strings (Dumont et al., 2012), cancer cell membrane (Zhang et al., 2020b), and viruses (Zhang et al., 2017) was developed, which can significantly improve the selectivity of Ln³⁺-containing NIR-II nanoprobes toward specific targets and enhance their targeting efficiency. For instance, human serum albumin (HSA) was modified on the surface of NaYF₄:Yb³⁺, Er³⁺@NaYF₄ NPs and magnified the accumulation of the NPs in tumor tissue by more than 10 times as compared with the uncoated counterparts (Naczynski et al., 2013). Furthermore, by controlling the thickness of albumin encapsulation, the biodistribution of the NPs can be modulated.

In current NIR-II luminescent imaging-guided surgery practice, photostable probes with long tumor retention period are favorable. Accordingly, Wang et al. (2018b) reported that the in vivo assembly of
complementary DNA modified NaGdF₄:Nd³⁺@NaGdF₄ nanoprobes may alter the tumor retention kinetics in a good manner and improve staging and debulking efforts in surgery. In their work, the ligand exchange strategy was utilized to realize the surface functionalization of NaGdF₄:Nd³⁺@NaGdF₄ NPs with complementary DNA. After being covalently anchored with the specific tumor peptide for improved targeting efficiency, these nanoprobes that can assemble efficiently, showed great potential in the application for intraoperative tumor-specific NIR-II imaging. Recently, cancer cell membrane was reported to modify NaYF₄:Nd³⁺@NaYF₄ nanoprobes for improved performance in tumor detection and tumor surgery navigation. Cancer cell membrane can camouflage nanoprobes to avoid fast clearance and macrophage (Zhang et al., 2020b). Thus, such cancer-cell-membrane coated nanoprobes exhibited significantly higher accumulation in the tumor and significantly enhanced blood retention compared to the counterparts with PEG encapsulation. These NIR-II nanoprobes with good tumor targeting ability further improved the tumor imaging quality in NIR-II imaging-guided surgery, showing the potential for clinical translation.

For in vivo molecular imaging, the non-invasive visualization of the disease biomarker can be realized by the conjugation of antibodies to Ln³⁺-containing NIR-II luminescent nanoprobes. As an example, AMD-3100 can be adsorbed onto the surface of above-mentioned HSA coated NaYF₄:Yb³⁺, Er³⁺@NaYF₄ NPs to further target the cancer biomarker of CXCR4 (Kantamneni et al., 2017). Thus, the AMD-3100 modified nanoprobes can label the lesions at distinct organ sites. In another example, amine groups modified NaYbF₄:Er³⁺, Ce³⁺, Zn²⁺@NaYF₄ NPs were conjugated with anti-PD-L1 mAb (i.e., monoclonal anti-bodies of Programmed Cell Death-Ligand 1) through 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) chemistry (named ErNPs-aPDL1) (Zhong et al., 2019). This ErNPs-aPDL1 NIR-II nanoprobe was employed for dynamic monitoring and assessing of PD-L1 heterogeneity in tumor. Furthermore, the agents that involve in biochemical reactions related to the biomarkers of physiological abnormalities can also be conjugated to Ln³⁺-containing NIR-II nanoprobes. For example, GSH that can respond to reactive oxygen species was selected to functionalize NaGdF₄:Nd³⁺@NaGdF₄ NPs for the precise bioimaging of inflammation (Zhao et al., 2019).

SUMMARY AND OUTLOOK
Ln³⁺-containing NIR-II luminescent nanoprobes have received extensive interest in recent years because of their excellent physicochemical characteristics, which make them intriguing candidates for diverse areas of bioimaging, biosensing, and imaging-guided therapy. Their optical properties can be modulated through tailoring a variety of parameters. As a result, this novel class of luminescent nanoprobes, while being in its infancy, has been rapidly developed and pushed forward to a new horizon for bioapplications in the NIR-II region. Substantial progresses have been gained from their fundamental photophysics to ingenious design strategies. Nevertheless, it remains several challenges to be solved in an effort to fulfill the requirements of commercial applications.

First, the NIR-II luminescence of Ln³⁺-containing nanoprobes results from several ET pathways due to the rich energy levels of Ln³⁺ and complex crystal environment. Therefore, a comprehensive investigation of the excited-state dynamics of Ln³⁺ is a prerequisite for rationally modulating and optimizing the optical properties of Ln³⁺-containing nanoprobes. To this end, fundamental studies through the high-resolution PL spectroscopy, time-resolved PL spectra, transient absorption spectra are urgently needed to elucidate the relationship between the composition/microstructure of the hosts and NIR-II luminescence of Ln³⁺ ions.

Second, one of the key bottlenecks for Ln³⁺-containing NIR-II nanoprobes is the relatively low PLQYs caused by the intrinsic low absorption cross section of Ln³⁺, which may cause poor temporal resolution and low sensitivity of biosensing. It should be noted that most of the current hosts are relatively inert, which are incapable of sensitizing the NIR-II luminescence of Ln³⁺ emitters. As such, there is still much room to optimize the optical properties of Ln³⁺-containing NIR-II nanoprobes. Sustainable efforts should be paid to explore more innovative hosts (e.g., QDs, metal-organic frameworks) and sensitization strategies so as to improve the PLQY of Ln³⁺-containing NIR-II nanoprobes. In addition, lifetime-engineered luminescent nanoprobes are getting rising attention in multiplexing imaging for eliminated signal loss and distortion in deep tissues. Nevertheless, approaches for lifetime probes with excellent sensitivity and fast feedback are lacking of exploiting. To seek the way, continuous efforts are needed to work on the precise synthesis and controlled lifetime responsiveness of these probes.
Thirdly, for Ln$^{3+}$-containing NIR-II nanoprobes, their biocompatibility and long-term toxicity are the key factors for clinical translation, which still lack thorough investigations. A systematic and general standard should be established to evaluate the performance of these probes in vivo. Although various surface modification methods have been employed to illustrate the promise of Ln$^{3+}$-containing NIR-II nanoprobes in biodetection and bioimaging, the undesired side effects including toxicity and the long-term stability of Ln$^{3+}$-containing NIR-II nanoprobes should be eliminated prior to their use for in vivo bioapplications. To this end, more kinds of bioactive agents coating are expected to be further exploited. Moreover, fundamental studies of surface chemistry including surface interactions, surface charge, and surface functionality are still highly demanded for controllable surface engineering.

Last but not the least, most of the current NIR-II imaging techniques based on conventional single-modal NIR-II luminescent nanoprobes do not fully satisfy the clinical requirements. For NIR-II luminescent nanoprobes, it remains a challenge to provide sufficient anatomical information due to the limited tissue detection depth and poor quantification capability. To meet the demands of up-to-date biotechnology, the exploration of multimodal bioprobes by combining other emerging modalities (e.g., magnetic resonance imaging, X-ray computed tomography imaging and photoacoustic imaging) with NIR-II luminescence of Ln$^{3+}$-containing nanoprobes is essential to accelerate their clinical translation. It should be noted that the NIR-II imaging studies associated with drug treatment have been rarely reported. The strategies for the construction of multimodal Ln$^{3+}$-containing NIR-II luminescent nanoprobes, which provide better data integration and validated results of each single-modal technique, will facilitate the precise therapeutic applications.

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AUTHOR CONTRIBUTIONS

Conceptualization, Y. J. Y., D. T. T., and X. Y. C.; Investigation, Y. J. Y., Q. Z., and P. Z.; Writing–Original Draft, Y. J. Y. and D. T. T.; Writing–Review & Editing, Y. J. Y., D. T. T., Y. Q. Z., X. Y. C.; Supervision, X. Y. C. and D. T. T.; Funding Acquisition, X. Y. C. and D. T. T.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

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