

MINI-REVIEW

Recent progress on lanthanide scintillators for soft X-ray-triggered bioimaging and deep-tissue theranostics

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Abstract

Lanthanide scintillators capable of converting the absorbed X-ray photon energy to ultraviolet (UV) or visible light, are emerged as promising nanoprobe for multifunctional diagnosis and deep-tissue antitumor therapy such as X-ray-excited fluorescence (XEF) imaging, X-ray-triggered photodynamic therapy (X-PDT), and soft X-ray-activated NO gas therapy. Such biomedical tools have the potential to overcome the major challenge of the depth barrier suffered by traditional optics. Recently, various lanthanide scintillators have been designed for diagnosis and therapy of deep-seated tumors. This minireview presents an overview of recent progress on the lanthanide-based scintillators and illustration of the potential challenges and future development.

1 | INTRODUCTION

Lanthanide-doped nanomaterials with excellent downshifting and novel upconversion (UC) emissions ranging

from UV to near infrared light (NIR) are considered as ideal nanoagents for applications in various fields, especially in bioapplication such as imaging and cancer therapy.^[1–10] However, most of the developed

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lanthanide-doped nanomaterials are triggered by UV or NIR light.^[1–10] Due to the relatively large absorption and scattering of photons in tissues, traditional light source (UV/visible/NIR)-activated lanthanide-doped nanomaterials suffered from the limitation of shallow penetration depth, resulting in low detection sensitivity and treatment efficiency.^[11] Alternatively, compared with the UV and NIR light, X-ray light presents the advantages of unlimited penetration depth, which can be used as a promising new excitation source for deep-seated bioimaging and antitumor treatment.^[12] In addition, some nanomaterials with high atomic number (*Z*) (named as scintillators) can be used as phototransducer for converting soft X-ray radiation into UV, visible, or NIR emission.^[13–20] Fortunately, lanthanide scintillators with large X-ray absorption efficiency not only possess excellent downshifting/UC emission,^[5–9] but also present outstanding radioluminescence, which are emerged as new typed agents for XEF imaging^[21] by using radioluminescence in visible light region. Besides, lanthanide scintillators can also be applied in X-ray-excited NIR-II imaging by using the XEF emission beyond 1500 nm with high resolution and sensitivity.^[22] Apart from the XEF bioimaging, lanthanide scintillators with efficient XEF can activate photosensitizers (PSs) to generate $^1\text{O}_2$ for deep-tissue X-ray-activated photodynamic therapy (X-PDT) based on fluorescence resonance energy transfer (FRET) effect.^[23,24] Moreover, lanthanide scintillators can also be used as soft X-ray-activated phototransducer for deep tissue on-demand controlled gas generation via combining photoresponsive gas releasing molecules, providing a novel deep-tissue antitumor strategy using low-dosage soft X-ray activatable gasotransmitter.^[25]

This minireview will outline the recent progress on the lanthanide scintillators for soft X-ray-triggered bioimaging and deep-tissue antitumor theranostics. We first focus on the XEF imaging and X-ray-excited NIR-II imaging with high resolution and sensitivity. Then, we will summarize the recent advances of lanthanide scintillator in antitumor theranostic applications including X-PDT and NO gas therapy.

2 | LANTHANIDE SCINTILLATORS IN XEF BIOIMAGING

2.1 | Radioluminescent mechanism of lanthanide scintillators

In principle, X-ray-activated radioluminescence process of lanthanide scintillators involves three consecutive stages, namely conversion, transport, and luminescence.^[26–30] At the initial conversion stage, upon X-ray irradiation, numerous high-energy electrons and holes are generated and afterwards electronic transport occurs in the inner shell

of atoms via photoelectric effect and Compton scattering. Subsequently, the hot electrons and holes are then quickly thermalized in the conduction and valence band edges. Finally, at the luminescence stage, the trapping and radiative recombination of the electron and hole occurs, leading to efficient radioluminescence ranging from UV to NIR (Figure 1A). And, the XEF efficiency of lanthanide scintillators is also influenced by many factors such as size, morphology, crystalline phase, and core-shell structures. Up to now, various efforts have been devoted to developing lanthanide scintillators for addressing specific needs to improve the XEF performance (Table 1).

2.2 | XEF bioimaging

Optical imaging with the advantages of minimal invasiveness, real time response, and high sensitivity has been widely used for early detection of tumors.^[31–34] In recent years, various nanosystems, including quantum dots, organic molecules, lanthanide-doped nanomaterials, have been developed as imaging agents. However, almost all these nanosystems are triggered by UV/vis light, and therefore, present inherent drawbacks of poor autofluorescence and shallow tissue penetrated depth. Although, NIR light-activated nanosystems are able to improve penetrative ability in living tissues, there are still great challenges for clinic application.^[35] XEF imaging based on scintillating nanomaterials can convert X-ray radiation into UV-vis-NIR light. Due to the insignificant scattering and high soft tissue penetration of X-ray, XEF allows for deep optical imaging in vivo with high spatial resolution and negligible tissue autofluorescence.^[36–38] Kennedy et al. explored the X-ray-activated radioluminescence of $\text{NaGdF}_4\text{:Eu}$ scintillating nanoparticles for XEF bioimaging.^[21] The radioluminescent intensity from the hexagonal phase $\text{NaGdF}_4\text{:Eu}$ is higher compared to other Ba-based fluoride (Figure 1B). Zeng and Liu et al. developed the $\text{NaYF}_4\text{:Gd/Tb}$ nanorods as scintillators for radioluminescence imaging.^[39] The experimental results indicated that the radioluminescence intensity of $\text{NaYF}_4\text{:Gd/Tb}$ nanorods was highly dependent on the doping contents of Tb^{3+} . And, deep-tissue radioluminescence signal of $\text{NaYF}_4\text{:Gd/Tb}$ nanorods (up to 5 cm) was achieved under low-dose soft X-ray irradiation (Figure 1C). It is noted that the radioluminescence intensity of scintillator is highly depended on the X-ray absorption efficiency, which is mainly related to the atomic number *Z*. Therefore, it is significantly important to design lanthanide scintillators with enhanced radioluminescence for highly accurate and sensitive bioimaging, even for clinical applications. Yang et al. developed the $\text{NaGd(WO}_4)_2\text{:Eu}$ nanoprobe as scintillators to enhance the radioluminescence through introducing large *Z* of W element with higher X-ray absorption efficiency.^[40] Compared with

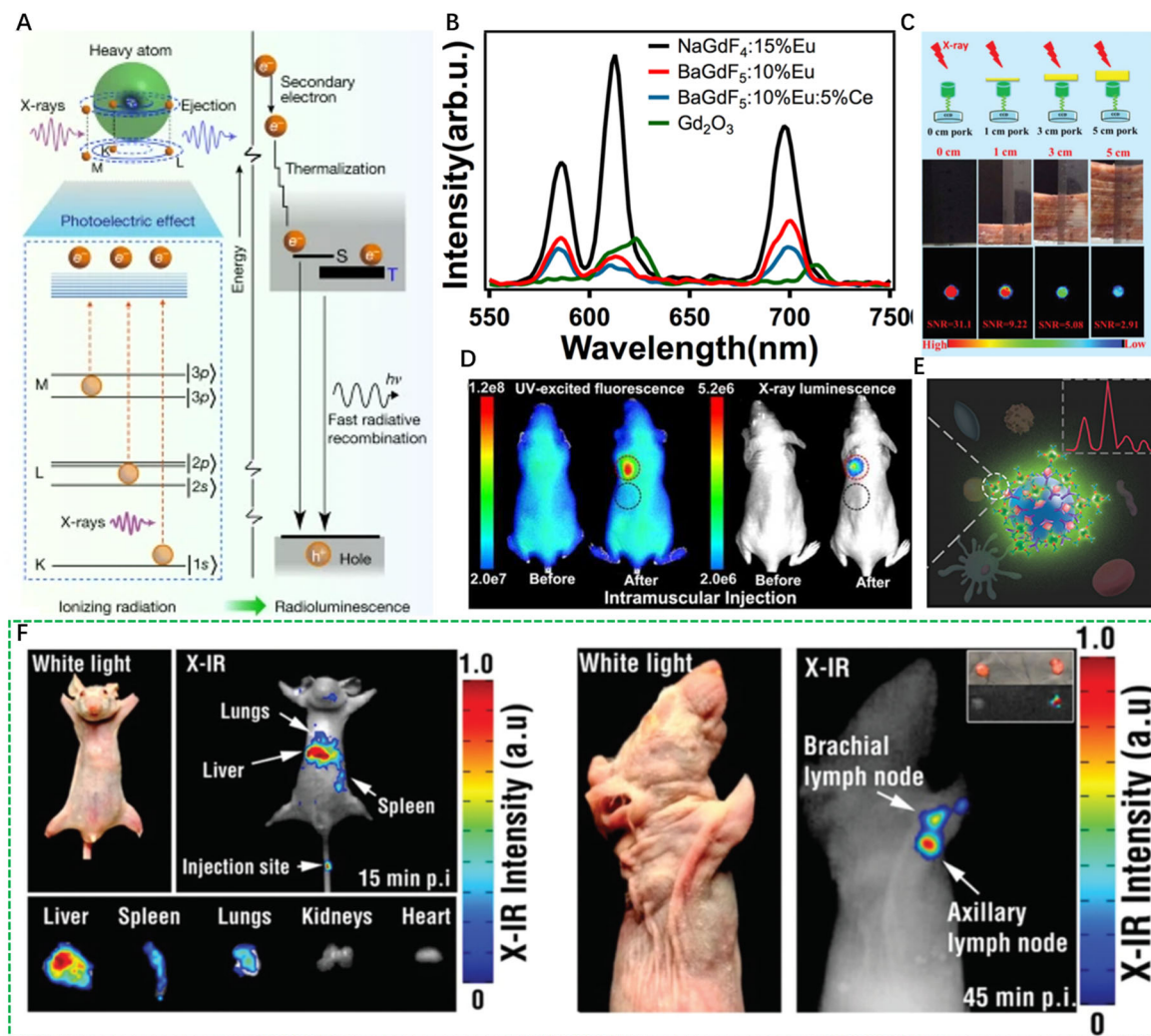


FIGURE 1 XEF bioimaging. (A) Schematic illustration of the radioluminescent mechanism of lanthanide scintillators.^[28] Copyright 2018, Nature Publishing Group. (B) X-ray excited radio-luminescence intensities from Eu³⁺ doped into different nanoparticle matrices.^[21] Copyright 2014, Royal Society of Chemistry. (C) XEF imaging of NaYF₄:Gd/Tb nanorods with different thicknesses.^[39] Copyright 2018, Royal Society of Chemistry. (D) red XEF bioimaging of mice before and after intramuscular injection of PEG-NaGd(WO₄)₂:Eu nanorods under UV and X-ray excitation.^[40] Copyright 2018, Royal Society of Chemistry. (E) X-ray excited radio-luminescence tags in X-ray luminescence immunoassay using NaGdF₄:Tb@NaYF₄ nanoparticles.^[42] Copyright 2018, American Chemical Society. (F) NIR-II XEF bioimaging based on lanthanide-doped nanoprobe.^[22] Copyright 2014, American Chemical Society

the previously reported scintillators (NaGdF₄:15%Eu^[21] and Gd₂O₃:18%Eu^[41]), the NaGd(WO₄)₂:Eu nanoprobe presented the highest radioluminescence intensity and radioluminescence intensity was improved about 2.4 times than NaGdF₄:15%Eu nanoparticles under identical X-ray irradiation conditions, which were further applied for *in vivo* XEF bioimaging (Figure 1D). In addition, Yang et al. demonstrated the NaGdF₄:Tb³⁺@NaYF₄ nanoparticles with 2.5 times enhancement of radioluminescence than NaGdF₄:Tb³⁺ via coating an inert shell to form core/shell structure.^[42] With the advantage of excellent radioluminescence intensity, the developed NaGdF₄:Tb³⁺@NaYF₄ scintillator was successfully applied to autofluorescence-free immunoassay (Figure 1E).

Although XEF imaging based on lanthanide scintillators has achieved great progress over the past years, the radioluminescent wavelengths of the developed XEF bioimaging applications are mainly centered at visible and NIR light region (<800 nm), remarkably impeding their further bioimaging applications. It is noted that NIR-II bioimaging by using emitting wavelength ranging from 1000 to 1700 nm is emerged as the next generation optical imaging technique owing to the reduced autofluorescence, attenuated photon scattering, and deep tissue penetration.^[43-48] Therefore, developing radioluminescence with emission located in NIR-II region is highly desirable for deep tissue and highly sensitive XEF bioimaging. Recently, a core-shell structured

TABLE 1 The explored lanthanide scintillators with different sizes for bioapplications

Lanthanide scintillators	Synthetic method	Size [nm]	Emission wavelengths	Bioapplications	Ref.
Tb ₂ O ₃	Hydro-/solvothermal	≈3.6 nm	488, 545, 588, and 625 nm	X-PDT	[62]
LaF ₃ :Ce	Hydro-/solvothermal	≈20 nm long and 5 nm wide	Approximately 520 nm	X-PDT	[64]
NaGdF ₄ :Eu	Hydro-/solvothermal	≈30 nm	About 587,612, and 700 nm	XEF bioimaging	[21]
NaGd(WO ₄) ₂ :Eu	Hydro-/solvothermal	≈402 ± 49 nm in length and 48 ± 8 nm in width	Approximately 615 nm	XEF bioimaging	[40]
NaGdF ₄ :Tb@NaYF ₄	Thermolysis	≈19.3 ± 1.3 nm	489, 546, 584, and 612 nm	Autofluorescence-free immunoassay	[42]
SrAl ₂ O ₄ :Eu	carbo-thermal reduction and vapor-phase deposition method	≈150 nm	around 520 nm	X-PDF	[66]
NaLuF ₄ :Gd/Eu@NaLuF ₄ :Gd@NaLuF ₄ :Gd/Tb	Thermolysis	≈28.9 ± 6 nm	488, 543, 590, 614, 695 nm	XEF bioimaging and X-PDT	[67]
NaYF ₄ :Gd/Tb	Hydro-/solvothermal	≈286 nm in length and 18 nm in width	489, 546, 584, 620 nm	Dual-modal XEF bioimaging	[39]
NaCeF ₄ :Gd/Tb	Hydro-/solvothermal	≈52.60 ± 11.46 nm in length and 18.87 ± 5.10 nm in width	490,545,577, 622 nm	Synchronous radio/Radiodynamic therapy	[68]
LiLuF ₄ :Ce	Thermolysis	≈70 nm	406 nm	Gas therapy	[80]

NaYF₄:Yb/Er@NaYF₄ nanoscintillator was developed with emissions beyond 1500 nm for deep NIR-II XEF bioimaging (Figure 1F), providing the first demonstration of NIR-II XEF bioimaging-guided lymphatic mapping.^[22]

3 | LANTHANIDE SCINTILLATORS FOR ANTITUMOR THERAPY

3.1 | Low-dose soft X-ray-triggered X-PDT

PDT, as a noninvasive and safe treatment, is emerged as an adjunct antitumor therapy strategy.^[49] There are three main components including excitation light source, oxygen, and PS required for efficient PDT.^[50] Under light irradiation, nontoxic PSs could convert light energy to nearby oxygen molecules for generating cytotoxic reactive oxygen species (ROS), such as singlet oxygen (¹O₂), leading to killing cancer cells.^[51-53] To date, most of the developed photo-activated PDT nanoplateforms are triggered by UV light. However, the UV-excited PDT suffered from the major limitation of low penetration depth of UV light in biological tissues.^[54] Then, to improve the penetration

depth, NIR light-activated PDT nanosystems have been designed.^[55-59] So far, the penetration depth in deep-tissue PDT achieved is usually below 1 cm, and therefore, the NIR light-triggered PDT still suffered from the relative low-therapy efficacy for deep-seated tumors.^[60] To this end, developing soft X-ray light-triggered PDT for breaking the limitation of the tissue penetration depth is emergently needed. In 2006, a photodynamic agent was reported by combining X-ray-activated scintillators with PS for tumor treatment.^[61] However, the limited XEF efficiency of scintillators remains a restriction for further bioapplications. Therefore, a combination of nanoscintillators with high XEF efficiency and PS has become a current focus of researches in this field. Since then, various X-PDT nanoagents integrating lanthanide scintillators (Tb₂O₃, Gd₂O₂S:Tb, LaF₃:Ce, LaF₃:Tb) with PSs have been designed.^[62-65]

Recently, Cheng and coworkers developed an X-ray-activated nanosystem based on SrAl₂O₄:Eu²⁺ (SAO) scintillator for deep-tissue X-PDT of tumor.^[66] In this system, successful ¹O₂ generation of the nanoscintillator was demonstrated under a low-radiation dose

(0.5 Gy) and presented the effective inhibition of U87MG human glioblastoma cells both in vitro and in vivo. Chang et al. designed a multifunctional core-shell-shell $\text{NaLuF}_4\text{:Gd/Eu@NaLuF}_4\text{:Gd@NaLuF}_4\text{:Gd/Tb}$ scintillator-based nanoplatfor for X-PDT application.^[67] The designed core/shell/shell nanoscintillator was employed as phototransducer to activate PS molecule (Rose Bengal, RB) for X-PDT through FRET. In this system, the radioluminescence from Tb^{3+} ion at 543 nm was used to produce $^1\text{O}_2$ under X-ray irradiation. And, red radioluminescence emissions at 614 and 695 nm from Eu^{3+} were applied for XEF imaging. Unfortunately, nanocomposites with combination of lanthanide scintillators and PS often present low loading capacity and leakage risk of PS, resulting in the limited X-PDT efficiency. Therefore, it is quite important to design high-efficiency X-ray-triggered nanoscintillator for direct ROS generation and PDT without loading PS. Recently, Chen et al.^[68] designed highly fluorescent $\text{NaCeF}_4\text{:Gd,Tb}$ nanoscintillator for X-ray excited radiodynamic therapy (RDT). In this study, Ce^{3+} ions act not only as sensitizers to improve the radioluminescence of terbium (Tb) ions under X-ray excitation but also as photocatalysts to induce the generation of superoxide anion ($\cdot\text{O}_2^-$) and hydroxyl radical ($\cdot\text{OH}$). It is expected that the lanthanide-based scintillator with efficient radioluminescence can be used as ideal phototransducer for low-dosage soft X-ray-triggered PDT, which can break through the barrier of the penetrated depth suffered by the traditional photoactivated PDT using UV/visible/NIR light.

3.2 | Soft X-ray-activated NO gas therapy

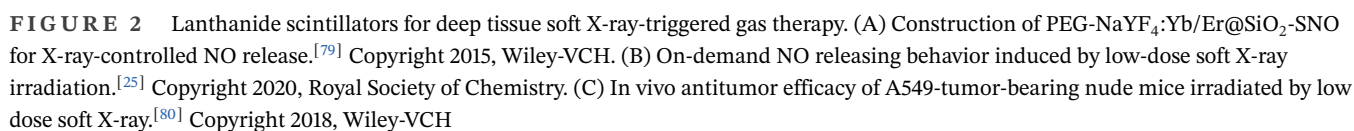
Gas therapy, including nitric oxide (NO), carbon monoxide, and hydrogen sulfide, is emerged as “green” therapeutic modality for tumors.^[69-72] And the controlled gas release in vivo is one of the key concerned problems for antitumor gas therapy.^[73] Therefore, developing stimuli-responsive gas releasing system with precise control is urgently demanded. Up to now, numerous stimuli-responsive NO/CO/H₂S donors have been developed for efficient gas delivery and controlled release of toxic gas.^[74-77] Due to the advantages of precise control of timing, location, and dosage, photo-triggered gas releasing platforms have been regarded as the promising stimuli-responsive gasotransmitter.^[78] Compared with the traditional UV and NIR light with limited tissue penetration, the X-ray light with high penetrated depth exhibits the unique advantage in controlled on-demand gas release for deep-tissue antitumor gas therapy. Recently, Shi and coworkers presented a pioneered study for design-

ing a multifunctional X-ray-responsive nanotheranostic system (PEG-USMS-SNO) for controlled gas therapy (Figure 2A).^[79] Owing to the low bond energy of S-N (150 kJ/mol), the S-N bond of the SNO group could be preferentially broken down by X-ray irradiation with dosage of (~5 Gy) to release NO molecules. Additionally, in vitro/vivo experiment results demonstrated the effective inhibition of tumor growth via NO gas release triggered by X-ray irradiation. Our group developed a new type of low-dosage soft X-ray-activated light transducer (Figure 2B) consisting of $\text{NaYF}_4\text{:Gd/Tb}$ nanorods and light-responsive NO donor Roussin's black salt (RBS) for depth-independent NO release and on-demand gas-sensitized cancer therapy via FRET.^[25] And deep tissue (up to 3 cm) NO gas release was achieved under low dosage of soft X-ray irradiation, leading to the inhibition of tumor growth in vivo. Recently, Zhao et al. developed a multifunctional X-ray-responsive NO release nanoplatfor (Figure 2C) by conjugating $\text{LiLuF}_4\text{:Ce}$ scintillators and RBS to control NO release.^[80] In this nanosystem, Ce-doped LiLuF_4 scintillators not only served as a PS for the generation of ROS, but also converted X-ray light energy into radioluminescence to activate RBS to generate NO, resulting in overproduction of ONOO^- for tumor treatment. In addition, in vivo therapy studies in A549 human lung tumor-bearing mice revealed obvious inhibition of tumor growth (Figure 2C). Thus, soft X-ray-triggered NO releasing nanoplatfor provides a new paradigm of depth-independent gaseous therapy for defeating deep-seated solid tumors in the future.

4 | CONCLUSIONS AND OUTLOOK

In this minireview, we have discussed recent progress on the lanthanide scintillators-based nanomedicine for soft X-ray-triggered bioimaging and deep-tissue antitumor therapy (X-PDT, RDT, and gas therapy). Particularly, soft X-ray-triggered NIR-II emission provides a new imaging tool for deep-tissue high-resolution XEF bioimaging by using the next-generation NIR-II optical imaging technique. Moreover, the low-dosage soft X-ray-activated PDT and gas-releasing nanoplatforms by using lanthanide scintillator-based light transducer provide a new strategy for deep-tissue antitumor therapy, overcoming the limitation of penetration depth suffered by the traditional UV or NIR light-activated systems.

Although the great advances in lanthanide scintillators for soft X-ray triggered bioimaging and deep-tissue theranostics are achieved, there are still several key challenges remained to be addressed for future biomedicine applications. First, the potential long-term toxicity of lanthanide scintillators with large size requires further



investigations. Thus, developing new lanthanide scintillators with ultrasmall size (<6 nm) and high XEF efficiency is highly desirable for high biocompatibility and fast degradable biomedicine applications. Second, high energy and high dosage X-rays are required for the X-ray-activated NIR-II bioimaging, subsequently resulting in radiation risk to normal biological tissues. Therefore, it is highly desirable to investigate the radioluminescence mechanism and search new strategies in order to further improve the XEF efficiency, especially in NIR-II radioluminescence for highly sensitive tumor imaging and therapy. Third, it is highly imperative to explore new methods for improving the tumor accumulation efficiency of the lanthanide scintillators and suppressing undesirable nonspecific uptake by normal tissues in antitumor therapy. Finally, there are still many issues and unknowns in lanthanide scintillator-based nanomedicines. Further studies for in-depth understanding of XEF mechanism, pharmacokinetics, biotoxicity, and interactions between lanthanide scintillator and biotissues are required for promoting the clinical translational of lanthanide scintillator in disease diagnosis and antitumor therapy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Z. G. Xia, A. Meijerink, *Chem. Soc. Rev.* **2017**, *46*, 275.
2. J. C. Zhou, Z. L. Yang, W. Dong, R. J. Tang, L. D. Sun, C. H. Yan, *Biomaterials* **2011**, *32*, 9059.
3. C. Yao, W. X. Wang, P. Y. Wang, M. Y. Zhao, X. M. Li, F. Zhang, *Adv. Mater.* **2018**, *30*, 1704833.
4. Y. B. Li, S. J. Zeng, J. H. Hao, *ACS Nano* **2019**, *13*, 248.
5. Z. G. Yi, X. L. Li, Z. L. Xue, X. Xiao, W. Lu, H. Peng, H. R. Liu, S. J. Zeng, J. H. Hao, *Adv. Funct. Mater.* **2015**, *25*, 7119.
6. F. Wang, Y. Han, C. S. Lim, Y. H. Lu, J. Wang, J. Xu, H. Y. Chen, C. Zhang, M. H. Hong, X. G. Liu, *Nature* **2010**, *463*, 1061.
7. L. Q. Xiong, T. S. Yang, Y. Yang, C. J. Xu, F. Y. Li, *Biomaterials* **2010**, *31*, 7078.
8. S. L. Gai, C. X. Li, P. P. Yang, J. Lin, *Chem. Rev.* **2014**, *114*, 2343.
9. Y. S. Liu, S. Y. Zhou, Z. Zhuo, R. F. Li, Z. Chen, M. C. Hong, X. Y. Chen, *Chem. Sci.* **2016**, *7*, 5013.
10. G. G. Lin, M. A. B. Baker, M. H. Hong, D. Y. Jin, *Chem* **2018**, *4*, 997.
11. W. P. Fan, W. B. Bu, J. L. Shi, *Adv. Mater.* **2016**, *28*, 3987.
12. D. Schaeue, W. H. McBride, *Nat. Rev. Clin. Oncol.* **2015**, *12*, 527.
13. L. Song, X. H. Lin, X. R. Song, S. Chen, X. F. Chen, J. Li, H. H. Yang, *Nanoscale* **2017**, *9*, 2718.
14. H. Q. Chen, D. C. Colvin, B. Qi, T. Moore, J. He, O. T. Mefford, F. Alexis, J. C. Gore, J. N. Anker, *J. Mater. Chem.* **2012**, *22*, 12802.
15. H. Y. Chen, T. Moore, B. Qi, D. C. Colvin, E. K. Jelen, D. A. Hitchcock, J. He, O. T. Mefford, J. C. Gore, F. Alexis, J. N. Anker, *ACS Nano* **2013**, *7*, 1178.
16. S. Som, P. Mitra, V. Kumar, V. Kumar, J. J. Terblans, H. C. Swart and S. K. Sharma, *Dalton Trans.* **2014**, *43*, 9860.
17. G. Pratx, C. M. Carpenter, C. Sun, R. P. Rao, L. Xing, *Opt. Lett.* **2010**, *35*, 3345.
18. Y. H. Zhang, R. J. Sun, X. Y. Ou, K. F. Fu, Q. S. Chen, Y. C. Ding, L. J. Xu, L. M. Liu, Y. Han, A. V. Malko, X. G. Liu, H. H. Yang, O. M. Bakr, H. Liu, O. F. Mohammed, *ACS Nano* **2019**, *13*, 2520.
19. J. H. Heo, D. H. Shin, J. K. Park, D. H. Kim, S. J. Lee, S. H. Im, *Adv. Mater.* **2018**, *30*, 1801743.
20. L. Song, P. P. Li, W. Yang, X. H. Lin, H. Liang, X. F. Chen, G. Liu, J. Li, H. H. Yao, *Adv. Funct. Mater.* **2018**, *28*, 1707496.
21. L. Sudheendra, G. K. Das, C. Q. Li, D. Stark, J. Cena, S. Cherry, I. M. Kennedy, *Chem. Mater.* **2014**, *26*, 1881.
22. D. J. Naczynski, C. Sun, S. Turkcan, C. Jenkins, A. L. Koh, D. Ikeda, G. Pratx, L. Xing, *Nano Lett.* **2015**, *15*, 96.
23. A. Kamkaew, F. Chen, Y. H. Zhan, R. L. Majewski, W. B. Cai, *ACS Nano* **2016**, *10*, 3918.
24. F. Ahmad, X. Y. Wang, Z. Jiang, X. J. Yu, X. Y. Liu, R. H. Mao, X. Y. Chen, W. W. Li, *ACS Nano* **2019**, *13*, 10419.
25. M. Y. Jiang, Z. L. Xue, Y. B. Li, H. R. Liu, J. H. Hao, *Nanoscale Horiz.* **2020**, *5*, 268.
26. M. Nikl, V. V. Laguta, A. Vedda, *Phys. Status Solidi B* **2008**, *245*, 1701.
27. M. Nikl, A. Yoshikawa, *Adv. Opt. Mater.* **2015**, *3*, 463.
28. Q. S. Chen, J. Wu, X. Y. Ou, B. L. Huang, J. Almutlaq, A. A. Zhumekenov, X. W. Guan, S. Y. Han, L. L. Liang, Z. G. Yi, J. Li, X. J. Xie, Y. Wang, Y. Ling, D. Y. Fan, D. B. L. Teh, A. H. All, O. F. Mohammed, O. M. Bakr, T. Wu, M. Bettinelli, H. H. Yang, W. Huang, X. G. Liu, *Nature* **2018**, *561*, 88.
29. T. K. Sham, S. J. Naftel, P. S. G. Kim, R. Sammynaiken, Y. H. Tang, I. Coulthard, A. Moewes, J. W. Freeland, Y. F. Hu, S. T. Lee, *Phys. Rev. B* **2004**, *70*, 045313.
30. K. Kiracki, P. Kubat, K. Fejfarova, J. Martincik, M. Nikl, K. Lang, *Inorg. Chem.* **2016**, *55*, 803.
31. Z. L. Xue, Z. G. Yi, X. L. Li, Y. B. Li, M. Y. Jiang, H. R. Liu, S. J. Zeng, *Biomaterials* **2017**, *115*, 90.
32. G. S. Hong, S. Diao, A. L. Antaris, H. J. Dai, *Chem. Rev.* **2015**, *115*, 10816.
33. S. Q. He, J. Song, J. L. Qu, Z. Cheng, *Chem. Soc. Rev.* **2018**, *47*, 4258.
34. O. S. Wolfbeis, *Chem. Soc. Rev.* **2015**, *44*, 4743.

35. G. Y. Chen, H. L. Qiu, P. N. Prasad, X. Y. Chen, *Chem. Rev.* **2014**, *114*, 5161.
36. C. M. Carpenter, G. Pratz, C. Sun, L. Xing, *Phys. Med. Biol.* **2011**, *56*, 3487.
37. D. M. Chen, S. P. Zhu, H. J. Yi, X. H. Zhang, D. F. Chen, J. M. Liang, J. Tian, *Med. Phys.* **2013**, *40*, 031111.
38. H. Y. Chen, M. M. Rogalski, J. N. Anker, *Phys. Chem. Chem. Phys.* **2012**, *14*, 13469.
39. X. L. Li, Z. L. Xue, M. Y. Jiang, Y. B. Li, S. J. Zeng, H. R. Liu, *Nanoscale* **2018**, *10*, 342.
40. T. Guo, Y. Lin, W. J. Zhang, J. S. Hong, R. H. Lin, X. P. Wu, J. Li, C. H. Lu, H. H. Yang, *Nanoscale*, **2018**, *10*, 1607.
41. A. D. Abid, D. S. Anderson, G. K. Das, L. S. Van Winkle, I. M. Kennedy, *Part. Fibre. Toxicol.* **2013**, *10*, 142.
42. X. Y. Ou, T. Guo, L. Song, H. Y. Liang, Q. Z. Zhang, J. Q. Liao, J. Y. Li, J. Li, H. H. Yang, *Anal. Chem.* **2018**, *90*, 6992.
43. G. S. Hong, A. L. Antaris, Dai, H. J., *Nat. Biomed. Eng.* **2017**, *1*, 0010.
44. G. S. Hong, S. Diao, J. L. Chang, A. L. Antaris, C. X. Chen, B. Zhang, S. Zhao, D. N. Atochin, P. L. Huang, K. I. Andreasson, C. J. Kuo, H. J. Dai, *Nature Photonics* **2014**, *8*, 723.
45. C. Y. Li, W. F. Li, H. H. Liu, Y. J. Zhang, G. C. Chen, Z. J. Li, Q. B. Wang, *Angew. Chem. Int. Ed.* **2020**, *59*, 247.
46. X. R. Song, S. H. Li, H. H. Guo, W. W. You, X. Y. Shang, R. F. Li, D. T. Tu, W. Zheng, Z. Chen, H. H. Yang, X. Y. Chen, *Angew. Chem. Int. Ed.* **2019**, *58*, 18981.
47. Y. Sun, F. Ding, Z. Chen, R. P. Zhang, C. L. Li, Y. L. Xu, Y. Zhang, R. D. Ni, X. P. Li, G. F. Yang, Y. Sun, P. J. Stang, *Proc. Natl. Acad. Sci. U.S.A.* **2019**, *116*, 16729.
48. D. J. Naczynski, M. C. Tan, M. Zevon, B. Wall, J. Kohl, A. Kulesa, S. Chen, C. M. Roth, R. E. Riman, P. V. Moghe, *Nat. Commun.* **2013**, *4*, 2199.
49. C. K. Lim, J. Heo, S. Shin, K. Jeong, Y. H. Seo, W. D. Jang, C. R. Park, S. Y. Park, S. Kim, I. C. Kwon, *Cancer Lett.* **2013**, *334*, 176.
50. J. F. Lovell, T. W. B. Liu, J. Chen, G. Zheng, *Chem. Rev.* **2010**, *110*, 2839.
51. Z. P. Zhen, W. Tang, C. L. Guo, H. M. Chen, X. Lin, G. Liu, B. W. Fei, X. Y. Chen, B. Q. Xu, J. Xie, *ACS Nano* **2013**, *7*, 6988.
52. W. Tang, Z. P. Zhen, M. Z. Wang, H. Wang, Y. J. Chuang, W. Z. Zhang, G. D. Wang, T. Todd, T. K. Cowger, H. M. Chen, L. Liu, Z. B. Li, J. Xie, *Adv. Funct. Mater.* **2016**, *26*, 1757.
53. Z. P. Zhen, W. Tang, M. Z. Wang, S. Y. Zhou, H. Wang, Z. H. Wu, Z. L. Hao, Z. B. Li, L. Liu, J. Xie, *Nano Lett.* **2017**, *17*, 862.
54. W. P. Fan, P. Huang, X. Y. Chen, *Chem. Soc. Rev.* **2016**, *45*, 6488.
55. Z. Y. Hou, Y. X. Zhang, K. R. Deng, Y. Y. Chen, X. J. Li, X. R. Deng, Z. Y. Cheng, H. Z. Lian, C. X. Li, J. Lin, *ACS Nano* **2015**, *9*, 2584.
56. M. Wang, Z. Chen, W. Zheng, H. M. Zhu, S. Lu, E. Ma, D. T. Tu, S. Y. Zhou, M. D. Huang, X. Y. Chen, *Nanoscale*, **2014**, *6*, 8274.
57. J. J. Peng, L. Z. Zhao, X. J. Zhu, Y. Sun, W. Feng, Y. H. Gao, L. Y. Wang, F. Y. Li, *Biomaterials* **2013**, *34*, 7905.
58. J. W. Tian, L. Ding, H. J. Xu, Z. Shen, H. X. Ju, L. Jia, L. Bao, J. S. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18850.
59. Z. J. Gu, L. Yan, G. Tian, S. J. Li, Z. F. Chai, Y. L. Zhao, *Adv. Mater.* **2013**, *25*, 3758.
60. J. L. Sandell, T. C. Zhu, *J. Biophotonics*, **2011**, *4*, 773.
61. W. Chen, J. Zhang, *J. Nanosci. Nanotechnol.* **2006**, *6*, 1159.
62. A. L. Bulin, C. Truillet, R. Chouikrat, F. Lux, C. Frochot, D. Amans, G. Ledoux, O. Tillement, P. Perriat, M. Barberi-Heyob, C. Dujardin, *J. Phys. Chem. C* **2013**, *117*, 21583.
63. Y. F. Liu, W. Chen, S. P. Wang, A. G. Joly, *Appl. Phys. Lett.* **2008**, *92*, 043901.
64. X. J. Zou, M. Z. Yao, L. Ma, M. Hossu, X. M. Han, P. Juzenas, W. Chen, *Nanomedicine* **2014**, *9*, 2339.
65. E. Abliz, J. E. Collins, H. Bell, D. B. Tata, *J. X-Ray Sci. Technol.* **2011**, *19*, 521.
66. H. M. Chen, G. D. Wang, Y. J. Chuang, Z. P. Zhen, X. Y. Chen, P. Biddinger, Z. L. Hao, F. Liu, B. Z. Shen, Z. W. Pan, J. Xie, *Nano Lett.* **2015**, *15*, 2249.
67. C. C. Hsu, S. L. Lin, C. A. Chang, *ACS Appl. Mater. Interfaces* **2018**, *10*, 7859.
68. X. Y. Zhong, X. W. Wang, G. T. Zhan, Y. A. Tang, Y. Z. Yao, Z. L. Dong, L. Q. Hou, H. Zhao, S. J. Zeng, J. Hu, L. Chen, X. L. Yang, *Nano Lett.* **2019**, *19*, 8234.
69. X. Zhang, G. Tian, W. Y. Yin, L. M. Wang, X. P. Zheng, L. Yan, J. X. Li, H. R. Su, C. Y. Chen, Z. J. Gu, Y. L. Zhao, *Adv. Funct. Mater.* **2015**, *25*, 3049.
70. Z. W. Lee, J. B. Zhou, C. S. Chen, Y. J. Zhao, C. H. Tan, L. Li, P. K. Moore, Deng, L. W., *PLoS One* **2011**, *6*, 0021077.
71. K. Kashfi, K. R. Olson, *Biochem. Pharmacol.* **2013**, *85*, 689.
72. D. W. Zheng, B. Li, C. X. Li, L. Xu, J. X. Fan, Q. Lei, X. Z. Zhang, *Adv. Mater.* **2017**, *29*, 1703822.
73. L. D. Yu, P. Hu, Y. Chen, *Adv. Mater.* **2018**, *30*, 1801964.
74. Y. Qian, J. B. Matson, *Adv. Drug Delivery Rev.* **2017**, *137*, 110–111.
75. H. J. Lee, D. E. Kim, D. J. Park, G. H. Choi, D. N. Yang, J. S. Heo, S. C. Lee, *Colloids Surf.* **2016**, *146*, 1.
76. Q. L. Song, S. W. Tan, X. T. Zhuang, Y. Y. Guo, Y. D. Zhao, T. T. Wu, Q. Ye, L. Q. Si, Z. Q. Zhang, *Mol. Pharmaceutics* **2014**, *11*, 4118.
77. V. Kumar, S. Y. Hong, A. E. Maciag, J. E. Saavedra, D. H. Adamson, R. K. Prud'homme, L. K. Keefer, H. Chakrapani, *Mol. Pharmaceutics* **2010**, *7*, 291.
78. M. J. Rose, P. K. Mascharak, *Coord. Chem. Rev.* **2008**, *252*, 2093.
79. W. P. Fan, W. B. Bu, Z. Zhang, B. Shen, H. Zhang, Q. J. He, D. L. Ni, Z. W. Cui, K. L. Zhao, J. W. Bu, J. L. Du, J. A. Liu, J. L. Shi, *Angew. Chem., Int. Ed.* **2015**, *54*, 14026.
80. Z. Du, X. Zhang, Z. Guo, J. Xie, X. H. Dong, S. Zhu, J. F. Du, Z. J. Gu, Y. L. Zhao, *Adv. Mater.* **2018**, *30*, 1804046.

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