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PERSPECTIVE

Lanthanide-Doped Upconversion Nanoparticles Meet the Needs for Cutting-Edge Bioapplications: Recent Progress and Perspectives

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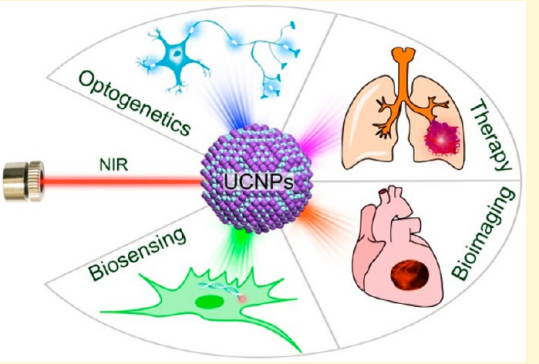
ABSTRACT: The rise of biological frontier fields such as precision theranostics, gene editing, optogenetics, etc. introduces the best opportunities and unprecedented challenges at the same time to the bioapplication of luminescent nanomaterials. Because of the merits of photon upconversion characteristics and high stability, tunable structure and excitation dynamics, and sharp emissions, the lanthanide-doped upconversion nanoparticle (UCNP) is considered to be a highly competitive candidate to meet these challenges. Indeed, UCNPs have attracted extensive attention in diverse cutting-edge bioapplication fields ranging from near-zero background biosensing, deep tissue bioimaging, precision nanomedicine, and remote biomanipulation since the first development in the early 2000s. Recently, with the increasing maturity of upconversion synthesis technology and the deep integration of multiple disciplines, the biological application research of upconversion has achieved many new breakthroughs. Herein, we summarize the latest bioapplication research progress of UCNPs in the fields of sensing, imaging, therapy, optogenetics, etc. Ultimately, current challenges and perspectives in this field are discussed.



For a long period of time, luminescent nanomaterials have been playing a significant role in biological and biomedical research fields.[1,2] In recent years, with the rise of precision therapy, gene editing, optogenetics and other frontier fields, the demand of the robust sensing platform for the precise analysis of physiological and pathological mechanisms, as well as sensitive profiling of disease biomarkers, the high-quality imaging contrast for discriminating deep-tissue lesions, the efficient therapeutic agent for accurate and specific treatments, and the intelligent regulation tool for spatiotemporal controllable cellular modulations is more urgent than ever.[3−5] This introduces the best opportunities and unprecedented challenges at the same time to the bioapplication of luminescent nanomaterials. However, the traditional luminescent nanomaterials based on photon downconversion emission strategy often possess the intrinsic drawbacks of poor photostability, susceptibility to background noise, and low tissue penetration ability, which make it difficult to meet the needs of the development of frontier biological science. Therefore, novel luminescent nanomaterials with excellent optical characteristics are highly necessitated to construct smart nanophotonic systems for diverse cutting-edge bioapplication scenarios.

Different from traditional downconversion emission, photon upconversion emission is a distinctive nonlinear optical process in which high-energy emission photons are generated by sequential absorption of two or more low-energy excitation photons via long-lived intermediate electronic states.[6] The idea of photon upconversion was first conceived by the Dutch−American physicist Nicolaas Bloembergen in 1959.[7] In the mid-1960s, this concept was realized and formulated independently by Auzel, Ovsyankin, and Feofilov, which was based on energy transfers between two different lanthanide ions (Ln^{3+}).[8] The bioapplication of photon upconversion emission was launched

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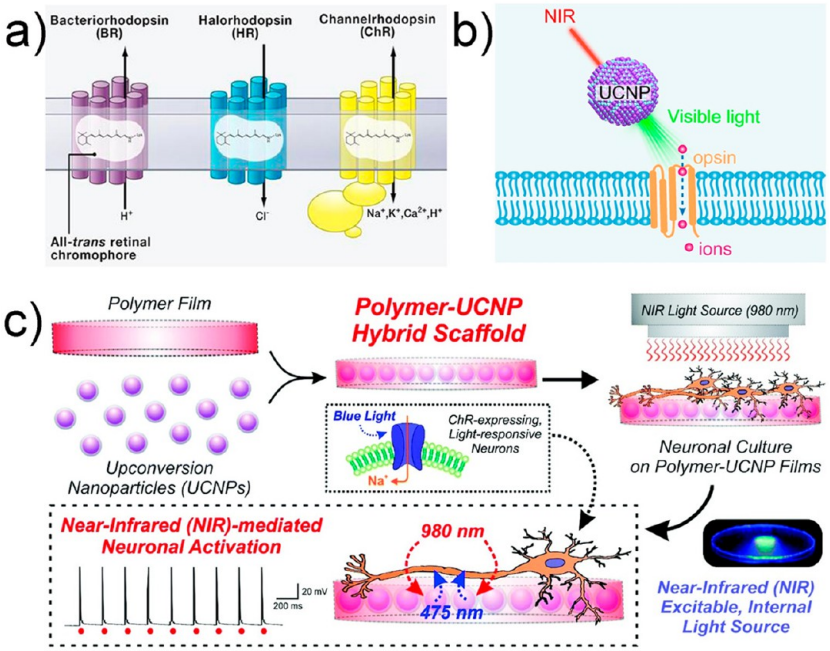

Figure 1. (a) Depiction of the three major classes of light-gated ion channels used for optogenetics. [Reprinted with permission from ref 26. Copyright 2011, Elsevier.] (b) Schematic of the principle of UCNP-mediated NIR optogenetics. (c) Schematic representation of the polymer−UCNP hybrid scaffold-assisted optogenetic neuronal activation. [Reprinted with permission from ref 33. Copyright 2015, Royal Society of Chemistry, London.]

in the 2000s, when nanotechnology greatly promote the controllable synthesis of high-quality lanthanide-doped upconversion nanoparticles (UCNPs) with the unique optical merits of large anti-Stokes shift, near-infrared (NIR) light excitation, high stability, tunable excitation dynamics, and sharp emissions.[9] These excellent luminescence characteristics well meet the demand for construction of advanced nanophotonic bioapplication platforms. Since then, UCNPs have been extensively utilized in diverse cutting-edge bioapplication fields, ranging from near-zero background biosensing, deep tissue bioimaging, precision nanomedicine, and remote biomanipulation.[10−12]

In recent years, with an in-depth understanding of the luminescence mechanism of UCNPs, scientists are better skilled in controlling the synthesis of UCNPs with specific luminescence properties.[13] For example, by synthesizing a multilayer core−shell structure and adjusting the type and ratio of the lanthanide dopants, the position and intensity of the emission peak can be precisely controlled, and even orthogonal emissions in response to two distinct NIR excitations can be achieved.[14] In addition, because of the rich energy level structures of the lanthanide ion, some special ion-doped upconversions can even possess efficient downconversion emissions that are located in the second near-infrared (NIR-II, 1000-1700 nm) window.[15,16] These new achievements in the synthesis have provided further advancement to the biological application research of UCNPs, including precise control of intracellular signaling and NIR-II emission-based deep tissue imaging.[17] At the same time, interdisciplinary integration has greatly promoted the use of UCNPs in more specialized biological fields, comprising optogenetics, visual neurophysiology, and cell biology.[18] Although some of these contents have been included in other precedent literature reviews,[19−23] in view of many brand new breakthroughs have been achieved in the past two or three years, it is necessary to conduct a systematic summary on the latest research on the bioapplications of UCNPs. This article will review the up-to-date application progress of UCNPs in the fields of biological detection, fluorescence imaging, optogenetics, etc., as well as evaluate the current challenges and perspectives.

OPTOGENETICS

Optogenetics modulation exploits light to extensively regulate the light-gated ion channels for the influx or outflux of ions, as well as to trigger the localization of protein onto the plasma membrane, enabling the precise and spatiotemporal modulation of the intrinsic cellular behavioral pathway.[24,25] Since opsin-associated ion fluxes are vastly comprehended for the detection and manipulation of targeted neurons, optogenetic approach utilizing deep penetrative wavelength of light has proven especially useful in the mechanistic study of the nervous system. To date, most of the conventional methods of optogenetics regulation on light-gated ion channels (such as Channelrhodopsin, Halorhodopsin, Bacteriorhodopsin, etc.) acquire the visible-light irradiation (Figure 1a).[26] These optogenetic operations window have gradually lapsed, because of their shallow tissue penetration depth upon visible-light exposure, which seriously impedes the application of optogenetics in vivo. The traditional method for in vivo optogenetic operation is to implant an external optical fiber into the animal brain to achieve light transmission.[27] Nevertheless, the external implanted optical fiber not only holds the apparent drawback, which restricts the animal movement, but also generates the perceptible debilitating force, which may cause irreversible injury to brain tissue, turning remote manipulation of ion channels or proteins by noninvasive method into a bottleneck to the development of optogenetics. As is well-known, the upconversion nanomaterials possess the optical characteristics of NIR excitation and visible-light emission, which ideally match the optogenetics demand for deep tissue penetration and visible light regulation (Figure

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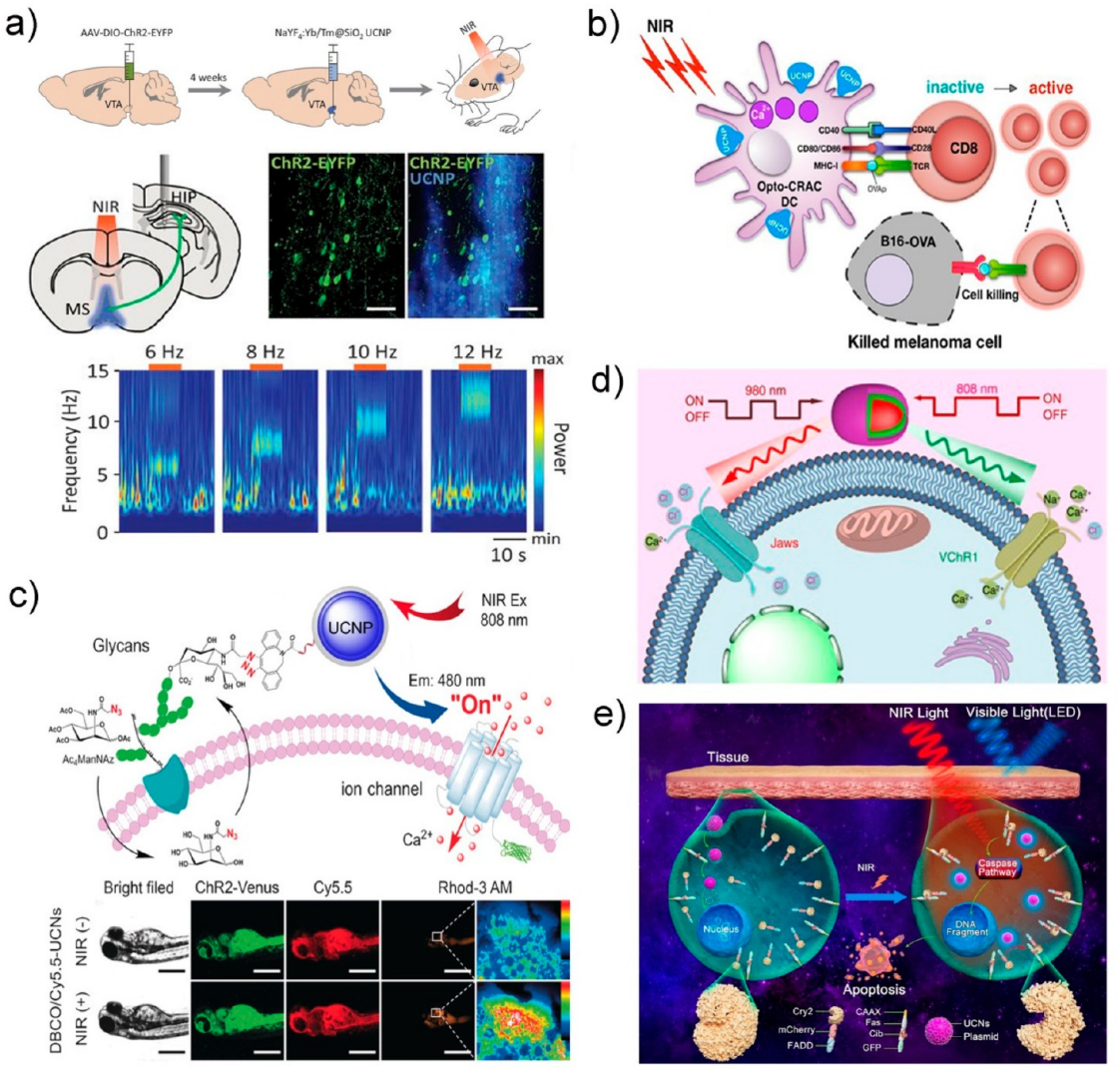

Figure 2. (a) Deep-brain stimulation through UCNP-mediated NIR optogenetics. [Reprinted with permission from ref 37. Copyright 2018, AAAS.] (b) NIR-activated Ca^{2+} influx prompts the maturation of Opto-CRAC DCs boosting antitumor immune responses. [Reprinted with permission from ref 39. Copyright 2015, eLife Sciences Publications, Ltd.] (c) Membrane localization of UCNPs for precise ion channel stimulation in zebrafish. [Reprinted with permission from ref 40. Copyright 2017, Wiley−VCH.] (d) Orthogonal activation of Jaws and VChR1 channels by 980 and 808 nm lasers. [Reprinted with permission from ref 41. Copyright 2019, Springer Nature.] (e) Upconversion optogenetic nanosystem mediated apoptotic signaling pathway controlling in cancer cells. [Reprinted with permission from ref 42. Copyright 2017, American Chemical Society, Washington, DC.]

1b).[28] Therefore, using upconversion materials is undoubtedly feasible and effective to solve the dilemma of remote optical transmission to obtain a potent optogenetic outcome.[29−32]

The application of UCNP-based optogenetics was firstly realized in 2015 by utilizing UCNP-doped film as a cell culture substrate for nerve cells regulation.[33,34] Hososhima and co-workers innovatively designed a film consisting of UCNPs for the evaluation of neuronal activity (Figure 1c). The optogenetic functionality of their UCNPs was tested against several opsins, including the C1 V1, mVChR1, and PsChR ion channels. After irradiation with NIR laser light (975 nm) from a remote-controlled fiber (diameter of 50 μm) in the patch electrode at a distance of 5.0 mm, the ion channels were activated to illustrate the potential for deep brain stimulation (DBS).[33] Shah et al. correspondingly synthesized a polymer-UCNP hybrid scaffold for optogenetic neuronal activation, by exposing the poly(lactic-*co*-glycolic acid)-UCNP film to the culturing of ChR-expressing neurons.[34] Latterly, Wu et al. introduced a NIR dye-sensitized UCNPs constructed by IR-806-sensitized $NaYF_4$:Yb^{3+},Er^{3+} UCNPs, which potently enhance the NIR-induced green-light intensity to accomplish the activation of channelrhodopsin.[35] This dye-sensitized UCNPs embedded cell culture film allows the precise temporal control of neuronal activation under NIR irradiation, since neuronal action potential is able to follow patterns of light pulses in a time-locked fashion.

These studies elaborately demonstrated the feasibility of photo-upconversion technology for NIR optogenetics. However, considering its deficient operability in vivo, NIR irradiation caused an overheating effect, and a potential biosafety issue caused by a high local concentration of UCNPs, such UCNPs-doping-film-based optogenetics form displayed an inadequate applicability in vivo. Hence, most of the recent UCNPs-based optogenetics studies are conducted through dispersed solution-phase systems. Bansal and co-workers originated a novel quasi-continuous wave (quasi-CW) NIR excitation of UCNPs for optogenetic manipulation, eliminating the drawback of the high

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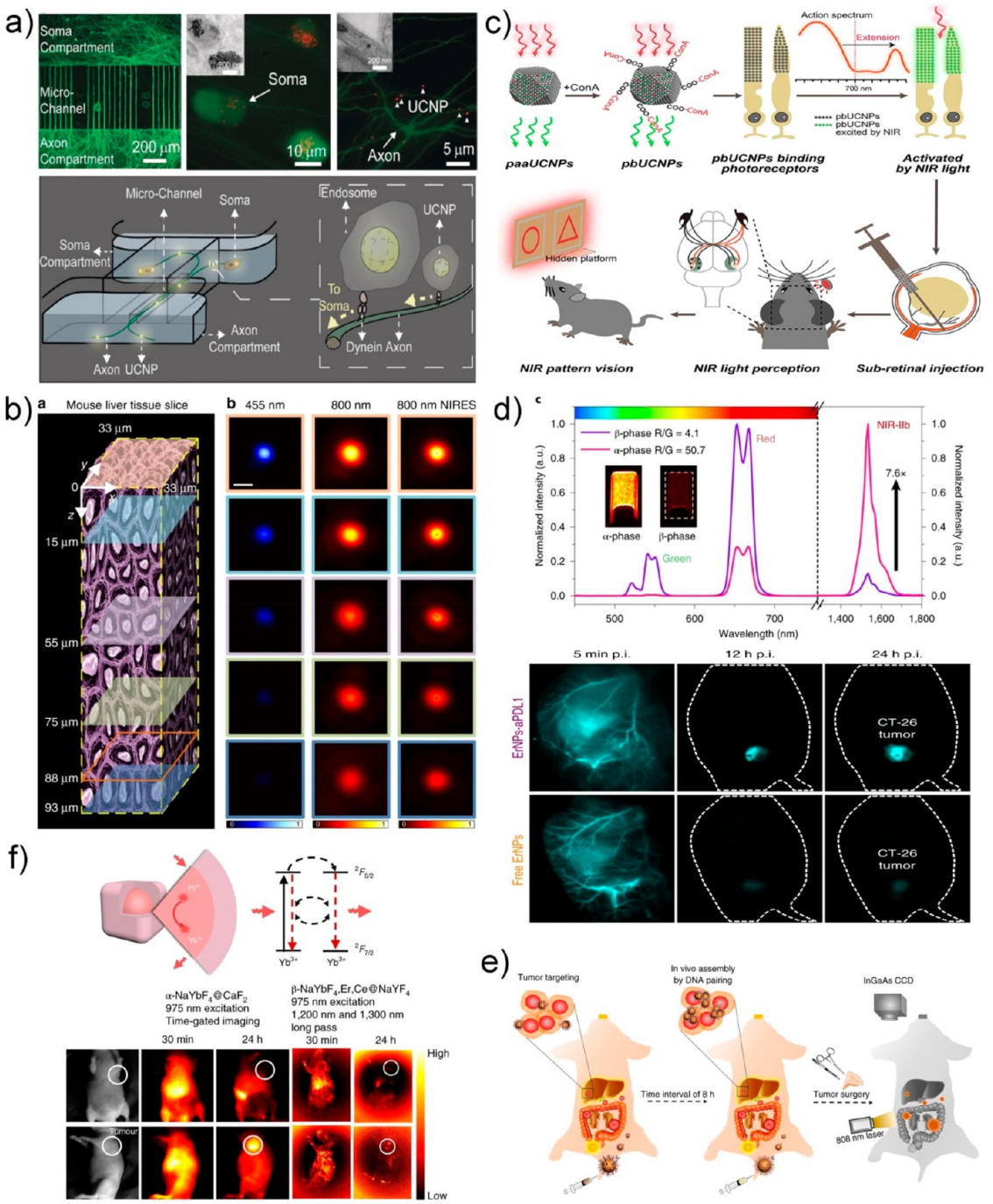

Figure 3. (a) UCNPs as an effective tool for displaying intraneuronal motor protein transport. [Reprinted with permission from ref 48. Copyright 2019, Wiley—VCH.] (b) The optical resolution of different methods for deep tissue imaging. [Reprinted with permission from ref 50. Copyright 2018, Springer Nature.] (c) UCNP-mediated NIR image vision in mammalian. [Reprinted with permission from ref 51. Copyright 2019, Elsevier.] (d) Deep tissue imaging for immunotherapy using NIR-IIb emission UCNPs. [Reprinted with permission from ref 56. Copyright 2019, Springer Nature.] (e) NIR-II image-guided surgery for metastatic ovarian cancer. [Reprinted with permission from ref 57. Copyright 2018, Springer Nature.] (f) High-sensitivity imaging in a UCNPs-based time-domain (τ) imaging model. [Reprinted with permission from ref 59. Copyright 2019, Springer Nature.]

excitation powers by the conventional CW excitation laser.[36] The optogenetic manipulations were successfully performed onto channelrhodopsins-2 (ChR2)-expressing *C. elegans*, represented by the activation of mechanosensory neurons via the blue light emitted by UCNPs upon NIR irradiation. Chen and co-workers reported 980 nm excited UCNPs employing the transcranial optogenetics to achieve deep brain stimulation (Figure 2a).[37] A blue-light-emitting $NaYF_4$:Yb/Tm@SiO_2 UCNPs was directly injected to a ventral tegmental area (VTA) of tyrosine hydroxylase (TH)-driven Cre recombinase (TH-Cre) transgenic mice. The Cre-dependent expression of ChR2 in dopamine (DA) neurons was optogenetically stimulated and striatal DA transients were attained to shed light on the treatment of major depression. Moreover, the UCNPs with green emission were established for neuron inhibition by matching the activation of halorhodopsin (NpHR)

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or archaerhodopsin (Arch). The hippocampal neurons were effectively silenced in the medial septum and the memory recall of awake mice was also realized by inhibition of hippocampal excitatory cells through NIR radiation, which elaborately verified the feasibility of optogenetic modulation by using UCNPs in vivo. Miyazaki et al. invented a "fiberless" approach by exploiting the lanthanide microparticles to depolarizing (C1 V1) and hyperpolarizing (ACR1) opsins for the manipulation of locomotive behavior of mice.[38]

All of the above articles are based on studies on the neural-related regulation of light-controlled ion channels. The regulation of ion channels has many other functions in cell physiology, such as activating immune cells, controlling the beat of cardiomyocytes and inducting tumor cell apoptosis. Similarly, UCNPs have also been used for optogenetically manipulating these different cell behaviors. He and co-workers presented a lanthanide-doped optogenetic platform (Opto-CRAC) with 980 nm excitation, which drives the gene transcription by controlling the isomerization of the blue-light-sensitive light-oxygen-voltage (LOV)-sensing domain.[39] The function of nonexcitable cells like T-lymphocytes was effectively regulated by modifying gene expression and immunomodulatory response (Figure 2b). Ai et al. reported a UCNP to accurately manipulate the light-gated channel activities to study physiological pathways.[40] The NIR-light-responsive UCNPs covalently localized onto the azido-tagged cell surface via copper-free click chemistry without modification of channel structure (Figure 2c). In addition, upon 808 nm laser excitation, the converted emission at 480 nm could successfully activate the light-gated ion channel, ChR2, thus controlling the calcium cation influx into cytosol remotely. Moreover, Ca^{2+}-dependent apoptosis was examined to be successfully modulated upon 808 nm irradiation. Notably, in vivo imaging was achieved by metabolic labeling of the zebrafish larvae in the abdominal cavity, indicating the effective manipulation of physiological activities in living animals. Mei and co-workers developed UCNPs with bi-orthogonal red and green emission upon NIR excitations to temporally regulate the two opsins of choice: the Jaws (halorhodopsin family) and VChR1 (channelrhodopsin family) ion channel proteins.[41] The precise bidirectional control can be attained by irradiating the UCNP-uptaken VChR1/Jaws-expressing tumor cells with a 808-nm laser for the green-light-responsive VChR1 to activate the influx of Ca^{2+} and 980 nm laser excitation for red-light-responsive Jaws for the influx of Cl^{-}(Figure 2d). The Ca^{2+} and Cl^{-} ions impact the membrane depolarization and hyperpolarization, respectively, and serve to on demand accelerate or decelerate the beating rate of cardiomyocytes, thus paving the way for therapeutic possibilities, such as molding programmable bidirectional optogenetic pacemakers.

Besides being employed for photogenetic regulation of ion channels, UCNPs are also used for photogenetic regulation of protein localization. For example, with the effort to non-invasively upregulate autophagy with spatiotemporal precision, Zheng et al. demonstrated the feasibility of using surface-modified UCNPs (UCNPs@(Fas-Cib+Cry2-FADD)) as the optogenetic nanosystem.[42] The classic apoptosis signal pathway molecule Fas and its adaptor molecule FADD were fabricated on the UCNPs as protein−protein interaction (PPI)-modulated plasmids, which could be endocytosed into the cytoplasmic space to perform apoptotic signals upon interval NIR irradiation (Figure 2e). More specifically, the on-and-off PPI interaction could be acquired in the tumor cells as well as in the living mouse model, representing a well-compacted model for NIR-controlled release of apoptotic signals. Adopting similar optogenetic PPI strategy but with the augmented design, Pan and co-workers facilitated the use of upconversion-rod-encapsulated flexible capsules (UCRs capsule) both in vitro and in vivo with upconverted blue emission.[43] Briefly, Cellular tumor antigen p53 was modified as a plasmid in the common optogenetics system Cry2-CiB1. Moreover, this model selectively achieves the p53 protein transportation from cytoplasm to nucleus under 980 nm excitation to induce cellular autophagy.

BIOIMAGING

Compared with traditional phosphors such as small molecule, fluorescence protein and quantum dots, UCNPs are undoubtedly a better choice for deep tissue and high-resolution fluorescence bioimaging.

Because of the rich energy level structures of lanthanide ions, the upconversion emission of UCNPs can be precisely adjusted from UV-Vis to first near-infrared (NIR-I, 700-950 nm) windows. In addition, by doping with specific lanthanide ions (such as Nd^{3+}, Ho^{3+}, Pr^{3+}, Tm^{3+}, and Er^{3+}), efficient down-conversion emission in the second near-infrared (NIR-II, 1000−1700 nm) window of UCNPs can be observed. These tunable characteristics of UCNPs provide more options for controlled bioimaging.[44−46]

UCNPs with efficient emissions in the visible region have been recently adopted as powerful tools for cellular dynamic tracing, measurement of intercellular environment viscosities, and even for creating the near-infrared image vision.[47] Zeng and co-workers made full use of the properties of UCNPs to propose a dynamic imaging technique, in which UCNPs was investigated as an effective and accurate tool for displaying axonal retromovement using multicompartment microcultured dorsal root ganglion (DRG) neurons (see Figure 3a).[48] Jin and co-workers built a novel approach to achieve single UCNP super-resolution imaging in living cells, which can be further used for measuring the intracellular viscosity.[49] They also reported the application of doughnut beam strategy to build near-infrared emission saturation (NIRES) nanoscopy for deep tissue observation of single UCNPs super-resolution imaging (Figure 3b).[50] Ma et al. overcame the limitations of mammalian vision by developing injectable photoreceptor binding upconversion nanoparticles (pbUCNPs) (Figure 3c).[51] These nanoparticles are attached to retinal photoreceptors to create NIR image vision as tiny NIR sensors. This innovative approach provides unparalleled opportunities for the design and application of a variety of new biointegrated nanodevices.

Compared to the deep tissue imaging in the visible-light and NIR-I window, the imaging in the NIR-II window often provides superior resolution, because of exponentially attenuating the light scattering and autofluorescence of tissue with the increasing wavelength from the visible-light to NIR-II window.[52] For example, in the imaging of mouse lymph vessels, the signal-to-noise ratio (SNR) changed from 1.4 to 1.3, 3.3, 7.3, and 10.5 as the imaging wavelength increased from 520 nm to 720, 1100, 1300, and 1500 nm.[53] Recently, with profound comprehension on the luminescence mechanisms, UCNPs with high NIR-II emission have been frequently reported and applied to different bioimaging scenes, in particular to the tumor imaging. Xue and co-workers developed polyacrylic acid (PAA)-coated $NaYF_4$:Gd/Yb/Er nanorods (PAA-NRS) with significantly enhanced NIR-IIB (1500−1700 nm) emission and good biocompatibility for brain vascular bioimaging and small tumor display in vivo.[54] By using the host−guest interactions

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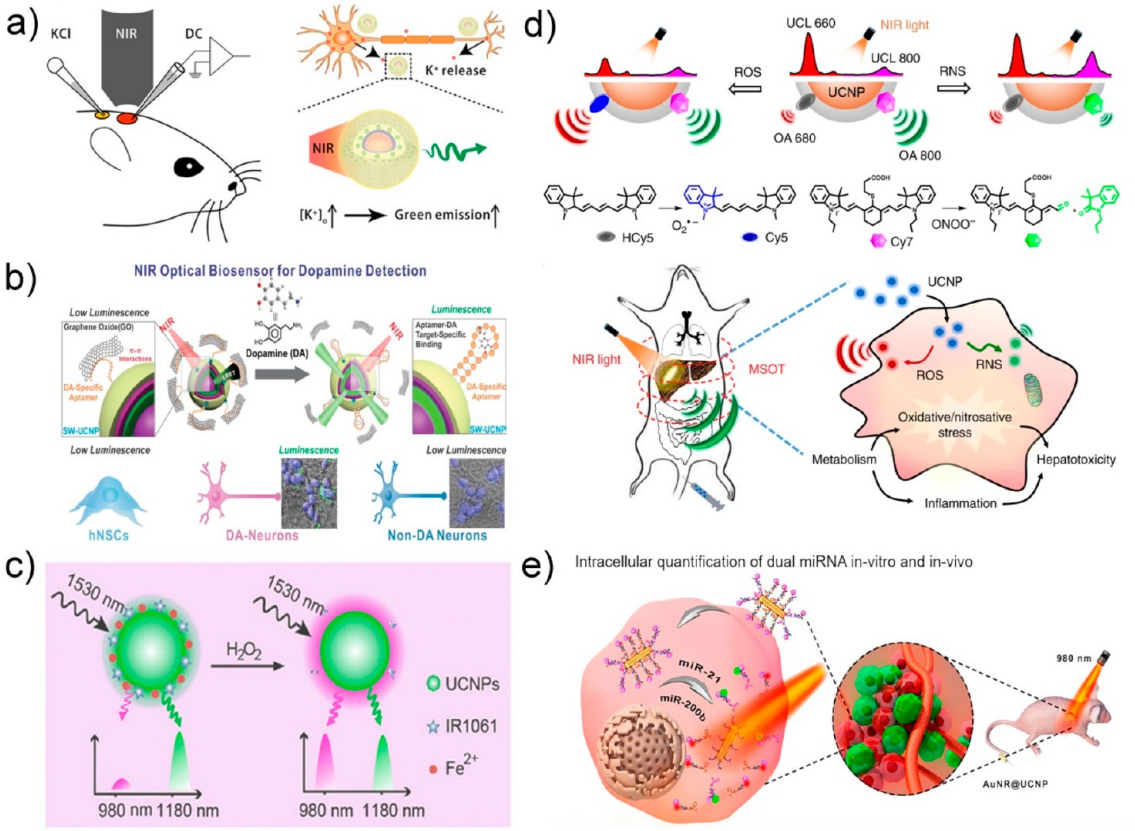

Figure 4. (a) UCNPs nanosensor for NIR potassium imaging. [Reprinted with permission from ref 61. Copyright 2020, AAAS.] (b) UCNPs for NIR biosensing of neurotransmitters in stem cell. [Reprinted with permission from ref 65. Copyright 2019, Wiley−VCH.] (c) NIR-II UCNPs for sensitive detection of H_2O_2 in vivo. [Reprinted with permission from ref 68. Copyright 2018, Wiley−VCH.] (d) Upconversion nanoprobes for dynamic redox correlation and pathophysiological progression imaging. [Reprinted with permission from ref 71. Copyright 2019, Springer Nature.] (e) Nanoparticle assemblies for miRNA cancer markers imaging at Zeptomolar level. [Reprinted with permission from ref 75. Copyright 2019, PNAS.]

between azobenzene and β-cyclodextrin, Zhao and co-workers developed an assembly state switchable UCNP in vivo for enhanced NIR-II imaging of tumors as well as accelerating the clearance of particles by the reticuloendothelial system (RES).[55] UCNPs-based NIR-II imaging has also been used for monitoring of tumor therapy process. Zhong and co-workers developed a biocompatible erbium-doped cubic phase (α-phase) UCNP emitting bright downconversion luminescence beyond 1500 nm (NIR-IIb region) for dynamic cancer immunotherapy imaging in mice (Figure 3d).[56] The nanoparticles were modified with anti-PD-L1 antibody for sensitive imaging of PD-L1 with a tumor-to-normal tissue signal ratio (T/NT ratio) of >40. The activation of cytotoxic T lymphocytes in tumor microenvironment and alteration of CD8 signals in spleen and tumor during the immunotherapy were demonstrated. Recently, Wang et al. developed a NIR-II image guided surgery method by using in-vivo-assembled UCPNs as the reporter.[57] Through the NIR-II image guidance, metastatic ovarian tumors can be clearly observed, thus achieving the accurate resection (Figure 3e). UCNPs have also been applied as codes for information encryption. Zhang and co-workers utilized the Tm^{3+}-sensitized UCNPs with lifetime tunable emission in the NIR-II window to build two-dimensional (2D) covert patterns for in vivo information storage and decoding, providing an ingenious multichannel coding concept.[58]

Aside from the imaging that was based on upconversion and downconversion emissions of UCNPs, Gu and co-workers recently developed a time-domain (τ) imaging model.[59] In this approach, the τ-dots (α-$NaYbF_4$@CaF_2) transduce short-pulse excitation photons into long-lived luminescent emission (Figure 3f). The prolonged luminescence can be discriminated from the same NIR spectral excitation by capturing with a time-gated luminescence spectral and imaging setup. Although the τ-dots used in the research is not an utterly optimized option, the time-domain (τ) imaging provide better results than the NIR-II imaging in a tumor-bearing mouse model.

All of these three imaging models based on UCNPs showed great bioapplication prospects and possessed their own unique advantages in biological imaging. For the upconversion imaging model, UCNPs own abundant upconversion luminescence bands in the UV-Vis-NIR I region to construct the desired imaging platforms for biological research and medical diagnosis, especially at the superficial tissue and the cellular level. The NIR-II imaging has more distinctive characteristics in deep-tissue imaging, because of its high tissue penetration ability. Theoretically, the imaging technology based on time domain (τ) imaging model can achieve exceedingly high fluorescence efficiency. Nevertheless, this technology is still in the early stage of exploration, thus more efforts are required to synthesize high-quality τ-dots and construct widely accepted imaging devices.

BIOSENSING

The various emissions, low autofluorescence, and high photostability of UCNPs also oil the wheels of the construction of

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reliable and sensitive biological detection platform. UCNP-based sensing platforms have been recently used for in vivo sensing of ions, small molecules, and reaction oxygen and nitrogen species, as well as important protein and nucleic acid biomarkers.

Recently, the recognition of ions fluctuation in organism has gained great attention, because of the decisive role of ions in physiological and pathological progresses. Peng and co-workers invented a UCNPs-based sensing platform by utilizing Zn^{2+}-sensitive chromophores-modified UCNPs as the probe for Zn^{2+} detection in zebrafish and in the brain slice of mice with Alzheimer's disease (AD).[60] Moreover, Liu and co-workers designed a specific and ultrasensitive NIR nanosensor for potassium.[61] The nanosensor was constructed by combining UCNPs with a commercial K^+ indicator and K^+-selective filter membrane, which performed as a transducer to convert NIR to UV light to activate the K^+ sensor potassium-binding benzofuran isophthalate (PBFI), thus achieving the detection of K^+ ion fluctuation in both cells and living animals (Figure 4a). Meanwhile, the nanosensor was also applied to explicitly image the cortical spreading depression (CSD) in an intact mouse brain, as well as to synergistically examine the extracellular potassium concentration and neuronal calcium activities in a zebrafish brain. Interestingly, the local field potential along with the optical signal can be simultaneously monitored by means of the cranial window.

Progress has also been made in the detection of various small molecules. For example, Peng and co-workers presented a dye-assembly nanoplatform to attain the rapid identification of hydrogen sulfide (H_2S).[62] The introduced nanoprobes were synthesized by combining designed sulfide-responsive chromophores with UCNPs, which were utterly applicable for ratiometric detection of H_2S molecule in live cells and in blood serum. By another path, Liu and co-workers reported a pure-inorganic upconversion nanoprobe by functionalizing Prussian Blue (PB) as a H_2S sensor, achieving sensitive and ultraselective H_2S detection, imaging, and elimination.[63] In addition, Lei et al. developed an exceedingly effectual NaCeF4:Er/Yb nanoprobe that exhibits NIR-II emission for delicate analysis of uric acid (UA) in human serum samples with the limit of detection as low as 25.6 nM.[64] Rabie and co-workers demonstrated a NIR dopamine sensing platform with an aptamer-modified core−shell−shell "sandwich" upconversion nanostructure (Yb@Er@Yb) as a probe (Figure 4b).[65] Using this platform, the dopamine secreted from the stem cell in differentiation could be selectively and sensitively monitored.

The precise detection of endogenous reactive oxygen and nitrogen species is an effective approach to understand the physiological processes such as immune or inflammatory response, cellular communication, and intermediary metabolism.[66,67] Liu and co-workers proposed a new type of H_2O_2-responsive Er^{3+}-sensitized UCNPs with both excitation (1530 nm) and emission (1180 nm) situated in the NIR-II window for in vivo inflammation dynamic evaluation (Figure 4c).[68] Peng et al. established a chromophore-modified UCNPs platform for "turn-on" luminescence sensing of peroxynitrite ($ONOO^-$) to evaluate acute hepatotoxicity in a mouse model.[69] By the same token, Zhao and co-workers reported a tumor-microenvironment $ONOO^-$-responsive nanosensor that conjugated with NIR-II dye for lifetime luminescence detection. By employing such a strategy, the recognition of hepatocellular carcinoma (HCC) can be accomplished by in vivo quantitative sensing with negligible thermal accumulation.[70] In recent study, Ai and co-workers presented an innovative strategy by combining unique NIR light-mediated upconverting nanoprobe with multispectral optoacoustic tomography (MSOT) imaging for reversed ratiometric acquisition of the dynamic reactive oxygen and nitrogen species (ROS/RNS) metabolism both in vitro and in vivo (Figure 4d).[71] Briefly, the NIR-light-mediated upconversion nanoprobe was prepared by individually coating two NIR cyanine fluorophores—ROS-responsive hydrocyanine substrate (HCy5) and RNS-responsive cyanine substrate (Cy7)—onto the upconversion nanocrystal surface. On the basis of radical stimulation, HCy5 and Cy7 went through the structural rearrangement or degradation as the response to radical oxidation, accounting for variations of both ratiometric upconverted luminescence and optoacoustic (OA) signals in NIR spectral region. This study arises a deep understanding in the pathophysiological roles of redox species in living animals, thus promoting the pathological interpretation of dynamic immune processes, as well as realizing the high-throughput drug screening in the pharmaceutical industry.

The sensitive detection of disease markers has colossal clinical significance for early diagnosis and understanding the dynamic change of diseases. Lately, various sensing platforms based on UCNPs have been developed for distinguishing different types of disease biomarkers, such as RNA, DNA, antigen, enzyme, etc.[72,73] For example, Chu et al. reported a photocage-based activatable hybridization chain reaction (HCR) strategy for spatially and temporally resolving signal amplification and ratiometric imaging of messenger RNA (mRNA) in vitro and in tumor tissues.[74] Qu and co-workers demonstrated UCNP and gold nanorod assemblies that, bridged by 5′-thiolated DNAs, can be an ultrasensitive detection platform for microRNA (miRNA) cancer markers (Figure 4e).[75] The detection limits of the both miRNA (miR-21 and miR-200b) were as low as the zeptomolar level. Song and co-workers developed a universal sensing platform by coating the hydrophobic UCNPs ($NaYF_4$:Yb,Er@$NaYF_4$) with single-layer grapheme oxide (GO).[76] As a proof-of-concept, this platform was used for the sensitive intracellular tracking and visualization of microRNA-21. Li and co-workers established a versatile UCNPs-PET platform with the luminescence quenching efficiency as high as 94.73%, which thus possess a high signal-to-background ratio (SBR) for sensitive detection of tyrosinase and alkaline phosphatase, as well as nerve agent simulant.[77] Aside from the disease biomarker recognition, UCNPs-based platforms for disease pathogen analysis have also been recently reported. Zhou and co-workers designed a series of special upconversion nanoparticles (τ_λ-UCNPs) with different luminescence emissions and decay lifetimes, which can construct more than 10^5 codes through color/lifetime binary strategy. This strategy was further demonstrated to be capable for simultaneous detection of human papilloma virus (HPV) subtypes in clinic samples, showing the clinical potential of UCNPs-based biosensing strategy.[78]

The detection mechanisms of these biosensing systems are mainly dependent on the change of energy transfer state between UCNPs and acceptor by targeting analyte, which leads to the change in the intensity of one upconversion emission band or in the intensity ratio between two bands.[79] Generally, there are two strategies for changing the state of the energy transfer by analytes, either modifying the spectra overlapping states or regulating the distances between acceptors and UCNPs.

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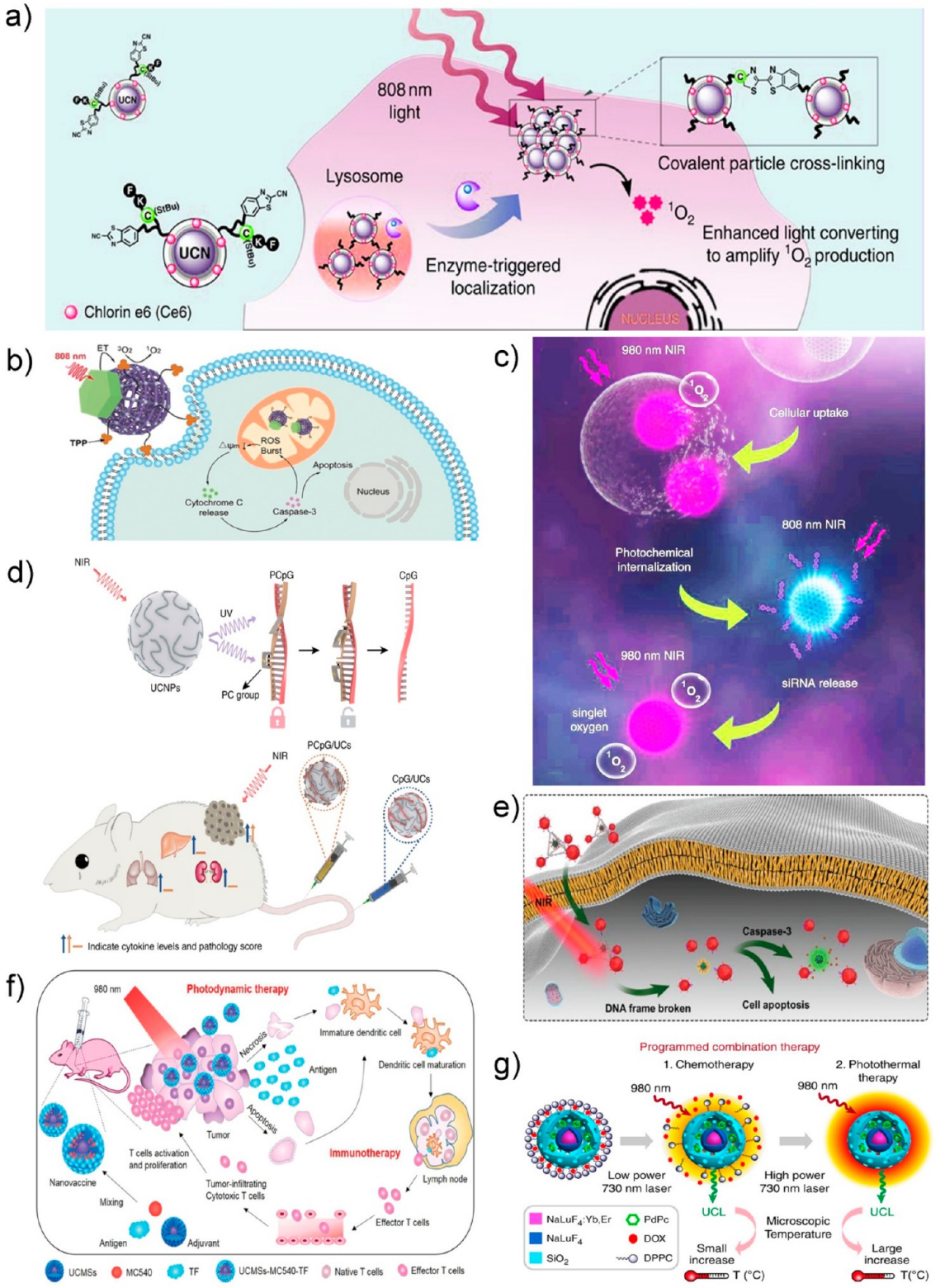

Figure 5. (a) In vivo cross-linking of UCNPs for precise tumour localization and theranostics. [Reprinted with permission from ref 86. Copyright 2016, Springer Nature.] (b) UCNP-MOF hybrids for mitochondria-targeted PDT. [Reprinted with permission from ref 87. Copyright 2020, Wiley–VCH.] (c) Programmable photoactivation of upconversion superballs for enhanced PDT. [Reprinted with permission from ref 89. Copyright 2019, Springer Nature.] (d) NIR-light responsive upconversion nanosystem for spatiotemporal triggering of anti-tumor immunity. [Reprinted with permission from ref 90. Copyright 2019, Springer Nature.] (e) NIR-controllable DNA-UCNPs nanotetrahedron for enhanced clearance of senescent cells. [Reprinted with permission from ref 91. Copyright 2020, Wiley–VCH.] (f) Upconversion nanoplatform as multifunctional immunoadjuvants for improved cancer photodynamic immunotherapy. [Reprinted with permission from ref 92. Copyright 2018, Wiley–VCH.] (g) Temperature-responsive UCNPs nanocomposite for precise programming combination cancer therapy. [Reprinted with permission from ref 93. Copyright 2018, Springer Nature.]

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THERAPY

The outstanding optical properties of upconversion nanomaterials allow it to possess broad application prospects in the imaging-based diagnosis and treatment of tumors and other diseases. Two main therapeutic strategies for UCNPs-based treatment are generally recognized as the photodynamic therapy (PDT), which produces toxic reactive oxygen species (ROS) utilizing upconverted ultraviolet or visible light, and the controlled release of chemotherapeutic drugs, immune antigens, and regulatory factors that are related to cell pathways exploiting upconversion light emission.[80−85] In recent years, upconversion has comprehensively attained a series of progress in precision therapy, vision therapy, synergistic therapy, etc.

Lately, Xing's group presented an innovated idea on site-specific antitumor PDT therapy with upconversion technology.[86] Their team prevailed a unique site-specific tumor treatment incorporating the peptide-premodified UCNPs (Figure 5a). The enzyme-responsive microenvironment-sensitive strategy has been adopted for specific localization of UCNs in the tumor cells. To elaborate, the 808-nm excitable Nd^{3+}-doped UCNPs were surface-modified with singlet oxygen-generating photosensitizer chlorin e6 (Ce6) and cathepsin B recognitive peptide sequence. Intracellular protein degradation was performed in a tumor microenvironment, because of the overexpression of lysosomal cysteine protease (cathepsin B). Upon encapsulation of the as-synthesized UCNPs by lysosome, as soon as cathepsin B recognized the peptide sequences present on the UCNs surface, peptide cleavage occurs, thereby triggering the site-specific accumulation of UCNs in the tumor site through covalent cross-linking. Consecutively, the built-up UCNPs excited by the 808-nm laser emit at a wavelength of 655 nm, as a result, prompting an amplified singlet oxygen generation for photodynamic therapy for tumor cell treatment. The cascade of reactions is thus rendered as a potential strategy for future biological ventures. Correspondingly, Liu et al. reported a mitochondria-specific upconversion metal-organic framework (MOF) with Janus nanostructure to achieve depolarization of mitochondrial membrane potential and initiation of apoptotic cascade by 808-nm-excitation-induced PDT.[87] Generally, the triphenylphosphine (TP) is functionalized at the UCNP surface as a mitochondria-target ligand, and the specific intracellular release of ROS by NIR irradiated photochemical reaction is corresponding to the production of pro-apoptotic protein cytochrome c, thus allowing the activation of caspase-3 to lead to the death of tumor cells (Figure 5b). Interestingly, upconversion system implanted with molecular photoswitch diarylethene (DAE) and porphyrinic PSs exhibited a promising treatment outcome in a programmable manner. Singlet oxygen generation is remotely controlled by 808-nm NIR light, accompanied by 980-nm NIR laser-managed photoswitching units, creating an off−on switchable PDT nanosystem to abate the systemic toxicity.[88] In addition, orthogonal photoactivable superballs were invented by Zhang's group, embedding the capability to enhance PDT efficiency with gene regulation.[89] Under individual radiation of 808/980 nm laser, the sensitivity toward ROS is increased by sequentially enhanced cellular uptake and photochemical internalization (PCI)-induced gene knockdown of superoxide dismutase-1, elucidating an innovative method to intensify the antineoplastic efficiency both in vitro and in vivo (Figure 5c).

NIR-based spatiotemporal controlled release of therapeutic agents, such as immune antigens, chemotherapeutic drugs, is one of the most promising strategies for the precision combatting cancer. Chu and co-workers designed a NIR-controlled immunodevice to remotely regulate the activation of anti-tumor immune responses.[90] Photocleaving the TLR9 agonist CpG-containing DNA that modified onto UCNPs by local UV light leads to the release of immunostimulatory agent CpG oligonucleotides (ODNs), thus contributing to the elevation of inflammatory cytokines production and immune T cells infiltration (Figure 5d). In recent studies, the therapeutic development of senescent cell treatment has also been demonstrated. Qu et al. constructed a gold chiral nanotetrahedron with a UCNP core by DNA self-assembly to realize the apoptosis of senescent cell.[91] Under NIR excitation, Granzyme B was released from this photocaged system to active the apoptosis-related downstream protease caspase 3, which could further be tracked by UCNP-connected fluorescent peptide CFDEVDK-Cy5.5 (Figure 5e).

Furthermore, synergistic therapy attracts the interest of researchers, which greatly improves the efficacy of anticancer treatment by the enhanced therapeutic effect. For example, in vivo vaccine delivery was innovatively attained by Lin's group.[92] The antitumor immune responses were effectively generated by localizing the nanovaccine, which was loaded with merocyanine 540 photosensitizers (MC540), chicken ovalbumin (OVA), and tumor cell fragment antigens (TF) into the tumor lesion, along with the significant proliferation of cytotoxic T lymphocyte cells under 980-nm irradiation (Figure 5f). Zhu and co-workers actualized the sequence control of chemotherapy and PDT by microscopically tuning the eigen temperature of designed UCNP under the alternating power density of 730 nm laser, harvesting 39-fold therapeutic enhancement in vitro (Figure 5g).[93] Inhibition of tumor growth by UCNPs-based immunotherapy was also accomplished by synergistically applying PDT and PTT (photothermal therapy). Yan et al. developed a chlorin e6 photosensitizer loaded core−shell UCNP with polydopamine (PDA) coating as a photothermal agent.[94] This dual-modal phototherapy shows potent ability to suppress the tumor metastasis in mice through the effective initiation of immunogenic cell death by triggering $CD8^+$ T lymphocytes.

Besides being utilized for cancer therapy, UCNPs also have recently employed to build powerful nanoplatforms for bacterial infection treatment, in which the PDT treatment is exploited as the main approach.[95−97] For instance, Zhang and coworkers built a NIR-activated UCNPs nanoplatform to eradicate multidrug-resistant (MDR) bacteria by using β-carboxyphthalocyanine zinc (CPZ) as a PDT photosensitizer.[98] Liu et al. fabricated rose bengal loaded $LiYF_4$:Yb/Er nanostructures for deep-tissue (∼5 mm) disinfection of acinetobacter baumannii (XDR-AB) upon 980-nm laser irradiation.[99] Xu et al. designed a Au/dark-TiO_2@UCNP plasmonic core−shell structure for enhanced NIR-assisted inactivation of ampicillin-resistant bacteria strains.[100]

OTHER BIOAPPLICATIONS

Besides afore-mentioned bioapplications of UCNPs, progress has also been made recently in other different biological application fields, such as photocage-based gene editor, photochromics-based bacterial regulation, photoresponsive artificial biosystem, photo-initiated bioorganic coupling, etc.

While the remote regulation of nucleic acid function is of great significance in clinical research, UCNPs-based photocage strategy has become an effective approach for the regulation of nucleic acid function, stem cell fate, etc.[101,102] Chu et al. used the

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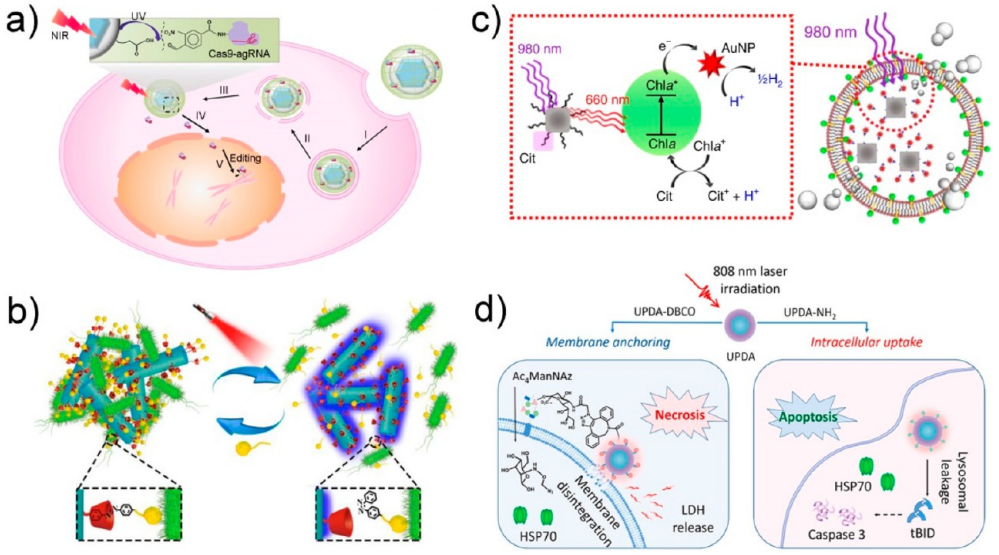

Figure 6. (a) UCNP-mediated NIR activation of CRISPR-Cas9 system. [Reprinted with permission from ref 103. Copyright 2019, AAAS.] (b) In vivo control of bacteria reversible clustering by NIR-driven multivalent UCNPs. [Reprinted from ref 107. Copyright 2019, with permission from Elsevier.] (c) Photosynthesis-inspired H_2 generation system for ROS detection and scavenging. [Reprinted with permission from ref 109. Copyright 2020, Springer Nature.] (d) Upconversion nanoplatform for indicating the position effect on cellular photothermal responses. [Reprinted with permission from ref 110. Copyright 2020, American Chemical Society, Washington, DC.]

UV emission of UCNPs to trigger the cleavage of a DNA hairpin structure and subsequently activate the hybridization chain reaction (HCR) in cells to perceive mRNA imaging within a specific organelle.[74] Pan et. al. developed a gene editing upconversion nanocage by utilizing advanced CRISPR-Cas9 technology.[103] In their work, UCNPs anchored with CRISPR-Cas9 by photocleavable 4-(hydroxymethyl)-3-nitrobenzoic acid (ONA) and PEI was successfully synthesized. Upon 980-nm laser activation, UCNP-Cas9@PEI showed robust on-demand control release of Cas9 protein to nucleus by emitting local UV light in cytoplasm, and the inhibition of tumor growth was realized by targeting PLK-1 cancer gene (Figure 6a). This work provides a new approach for targeted gene editing in deep tissues. Recently, Qu's group reported a UCNP-based NIR regulation approach for controlling the stem cell fate. Through adjusting the NIR laser power density, the cell−matrix interactions would be dynamically manipulated, thus inducing the differentiation of mesenchymal stem cell (MSC) to adipocytes or osteoblasts.[104]

Meanwhile, UCNPs-based photoswitch systems have been developed for bioregulation under NIR radiation.[105] Qu et al. proposed a photochromic spiropyran conjugated UCNP as a Pickering emulsifier, to accomplish reversible hydrophilicity/hydrophobicity surface inversion under NIR and visible light.[106] By applying such a strategy, the catalytic performance of biocatalytic active bacteria is highly enhanced through the immobilization of whole bacteria, and the substrate inhibition effect is significantly reduced to provide ideal product recovery features. Intriguingly, Qu and his team presented another upconverting nanosystem for dynamic regulation of bacteria interaction through the remote control of bacteria clustering behaviors (Figure 6b).[107] A macrocyclic host β-CD was introduced to UCNP to undergo a photoresponsive bacterial recognition process with azo-benzene glycoconjugates. The incessant isomerization of azo-man molecule results in desired dispersion and agglutination of bacterial clusters, and finally control the in vivo infectious diseases caused by pathogens.

The emissions of UCNPs have recently been proved to be an effective light source for photoreactions.[108,109] For example, in order to offer assistance to the cell defense system, Sung et al. introduced a smart H_2-generating upconversion nanoplatform to combat the reactive oxygen species (ROS) homeostasis disturbance (Figure 6c). Synergistic treatment of excess ROS detection and reduction in situ was attained by designing gold nanoparticle conjugated UCNPs, which was packaged inside the liposomal system with chlorophyll a in its lipid bilayer.[109]

Furthermore, Do and co-workers unveiled a molecular basis of photothermal responses through specific organelle localization of the polydopamine-coated photothermal upconversion nanoparticles (UPDA) to subcellular cell fractions (Figure 6d).[110] Under 808-nm light excitation, the heat generated by surface anchored UPDA-dibenzyl cyclooctyne (UPDA-DBCO) and intracellular uptaked UPDA-poly(ethylenimine) (UPDA-PEI) were monitored to understand the cellular heat response toward different thermal lysis modes. This study reveals the crucial dependence of photothermal nanoparticles localization on monitoring cellular responses upon NIR light, which is thus indispensable in personalized nanomedicine.

■ OUTLOOK

NIR-light-responsive lanthanide-doped upconversion nanoparticles (UCNPs) have made many breakthroughs in the traditional biological research fields, including molecular detection, biomedical imaging, and cancer therapy. In addition, the application of upconversion has been further advanced to more-specialized biological fields, such as cellular dynamic tracking and manipulation, optogenetics, immune regulation, and visual neurophysiology. These progressions have laid a concrete foundation for the further development of upconversion biological applications and galvanized more researchers in related field. Nonetheless, it is undeniable that most of the current research is still undergoing the proof-of-concept stage. For instance, while extensive studying the application of imaging, therapy, tissue-penetrable NIR light optogenetics,

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and other aspects, authors commonly verify the feasibility of the concept from the cellular level or living-small-animal level. However, almost all the currently used models are considerably incompatible from the real application scenes, and the clinical operability of the experimental process is also not ideal. In the next stage of research, the arising issues to be contemplated are as follows:

(1) How to make UCNPs-based nanoprobes that become research tools of molecular biology and reliable biological detection reagents as fluorescent molecular probes and fluorescent proteins

(2) How to make UCNPs-based nanocontrast agents and nanomedicine, to become the standard imaging reagent as well as a safe and effective nanodrug in clinical practice.

Making further breakthroughs in fundamental biomedical research and clinical translation requires the joint efforts of researchers from many aspects:

(i) Conduct biological effect assessment systematically. There is no doubt that, before UCNPs can be accepted in clinical application, their biosafety must be adequately validated. Although UCNPs are generally considered to possess hypotoxicity, the conclusion is usually made based on short-term findings at the cellular level or in small animals.[111,112] Long-term biological effects of UCNPs in vivo must to be further explored, such as long-term enrichment and aggregation behavior, influence on local ROS production and immune behavior of organs and tissues, as well as the influence on protein expression and molecular metabolism levels, etc. The excretion of UCNPs from the body is also a significant concern, with regard to its biosafety. As observed with most drugs, UCNPs are mainly excreted through the renal and hepatobiliary pathway. Generally, small UCNPs can be excreted quickly via the renal pathway within days or even hours, while large particles are excreted mainly through the biliary route, which takes several weeks or even years. However, different from small organic molecules, the structure and properties of UCNPs are more complex. So far, the excretion mechanism of UCNPs is far from clear. Futhermore, the selection of UCNPs should not be limited to a specific particle in the study of biological effects. It is also worth considering whether the difference in composition, surface charge, or modified group will have different biological effects. This would require systematic research, preferably to construct a database, which would provide clear insight into the biological effects of UCNPs and provide valuable guidance for further design.

(ii) Strengthen basic research on synthesis of UCNPs. Until now, although the application of UCNPs in mice showed acceptable results, it is still challenging to achieve similar outcoms in larger mammals, requiring UCNPs with much higher luminous efficiency under low power density excitation to avoid the background signal interference and hyperthermic injury. On the one hand, further studies of luminescence mechanism and understanding of luminescence processes are required to provide guidance for the design and synthesis of ideal UCNPs. For example, heavy lanthanide doping and fabrication of a multilayer core−shell structure are considered to be trustworthy ways to enhance upconversion efficiency under low-power-density excitation.[8,113] However, the rational design of these structures still remains a challenge, because of the incomplete understanding of light harvest, energy transfer, and cross-relaxation processes. On the other hand, we should actively explore how to enhance the luminescence efficiency through a coupling effect, such as plasma enhancement effects and dye sensitization enhancement effects.[114] Besides, it is necessary to perform systematic synthesis research and establish the database of UCNPs for both chemists and biologists. Furthermore, considering the cost and maneuverability for bioapplication, the method to achieve the low cost of mass synthesis should also be further studied.

(iii) Establish uniform standards. There is a problematic phenomenon that every article claims to have a good bioapplication performance when comparing the efficiency of UCNPs. However, it is impossible to compare which one performs better, because the measurement conditions varied in each design. It is a tremendous project to realize the ultimate goals of biological application research of UCNPs, which cannot be accomplished by one or two individuals or research groups, but rather requires the long-term joint endeavors of many research groups. Therefore, it is necessary to establish uniform standards. For example, in terms of evaluating the luminous efficiency, the quantum yield of UCNPs under specific conditions can be determined uniformly; in terms of imaging, the imaging SNR can be measured consistently through a specific thickness of tissue under a single excitation wavelength of the specific imaging reagent concentration and light intensity; in terms of therapy, a uniform concentration of nanodrugs, laser irradiation intensity, and duration can be prescribed.

(iv) Reinforce the development of detection and imaging devices. The commonly used spectrometers and imagers are sufficient for the proof-of-concept research in the laboratory. Nevertheless, the real application scene requires suitable supporting equipment. For example, portable spectrometers are needed for UCNPs-based outdoor on-line detections, and wearable imagers (imaging glasses, for example) are required for luminescence-guided surgeries. Close collaboration between the researchers involved in upconversion biological applications field and engineers in the field of optical devices is expected.

To summarize, the biological applications of upconversion nanomaterials have brilliant prospects, but also face plenty of challenges. It is believed that, through the cooperative efforts of researchers, the path of biological application of upconversion nanomaterials will become broader and brighter.

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Notes

The authors declare no competing financial interest.

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Bengang Xing received his Ph.D. degree from Nanjing University in 2000, after which he did his postdoctoral studies in HKUST, UCLA, and Stanford University. He joined Nanyang Technological University (NTU) in 2006. Currently, he is a full professor in the School of Physical & Mathematical Sciences and School of Chemical & Biomedical Engineering at NTU. His research interest is at the interface of biofluorescence imaging, chemical biology, and nanomedicine, focusing on the development of "smart" small molecules, peptides, and nanoprobes for biological process monitoring and diagnosis.

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■ REFERENCES

(1) Chinen, A. B.; Guan, C. M.; Ferrer, J. R.; Barnaby, S. N.; Merkel, T. J.; Mirkin, C. A. Nanoparticle Probes for the Detection of Cancer Biomarkers, Cells, and Tissues by Fluorescence. *Chem. Rev.* **2015**, *115*, 10530−10574.

(2) Wolfbeis, O. S. An overview of nanoparticles commonly used in fluorescent bioimaging. *Chem. Soc. Rev.* **2015**, *44*, 4743−4768.

https://dx.doi.org/10.1021/acsmaterialslett.0c00377
ACS Materials Lett. 2020, 2, 1516−1531

(3) Li, J.; Wang, L.; Tian, J.; Zhou, Z.; Li, J.; Yang, H. Nongenetic engineering strategies for regulating receptor oligomerization in living cells. *Chem. Soc. Rev.* **2020**, *49*, 1545−1568.
(4) Li, W.; Yan, Z.; Ren, J.; Qu, X. Manipulating cell fate: dynamic control of cell behaviors on functional platforms. *Chem. Soc. Rev.* **2018**, *47*, 8639−8684.
(5) Sang, W.; Zhang, Z.; Dai, Y.; Chen, X. Recent advances in nanomaterial-based synergistic combination cancer immunotherapy. *Chem. Soc. Rev.* **2019**, *48*, 3771−3810.
(6) Auzel, F. Upconversion and Anti-Stokes Processes with f and d Ions in Solids. *Chem. Rev.* **2004**, *104*, 139−174.
(7) Bloembergen, N. Solid State Infrared Quantum Counters. *Phys. Rev. Lett.* **1959**, *2*, 84−85.
(8) Chen, G.; Agren, H.; Ohulchanskyy, T. Y.; Prasad, P. N. Light upconverting core-shell nanostructures: nanophotonic control for emerging applications. *Chem. Soc. Rev.* **2015**, *44*, 1680−1713.
(9) Zhou, B.; Shi, B.; Jin, D.; Liu, X. Controlling upconversion nanocrystals for emerging applications. *Nat. Nanotechnol.* **2015**, *10*, 924−936.
(10) All, A. H.; Zeng, X.; Teh, D. B. L.; Yi, Z.; Prasad, A.; Ishizuka, T.; Thakor, N.; Hiromu, Y.; Liu, X. Expanding the Toolbox of Upconversion Nanoparticles for *In Vivo* Optogenetics and Neuromodulation. *Adv. Mater.* **2019**, *31*, 1803474.
(11) Loo, J. F.-C.; Chien, Y.-H.; Yin, F.; Kong, S.-K.; Ho, H.-P.; Yong, K.-T. Upconversion and downconversion nanoparticles for biophotonics and nanomedicine. *Coord. Chem. Rev.* **2019**, *400*, 213042.
(12) Rafique, R.; Kailasa, S. K.; Park, T. J. Recent advances of upconversion nanoparticles in theranostics and bioimaging applications. *TrAC, Trends Anal. Chem.* **2019**, *120*, 115646.
(13) Wen, S.; Zhou, J.; Zheng, K.; Bednarkiewicz, A.; Liu, X.; Jin, D. Advances in highly doped upconversion nanoparticles. *Nat. Commun.* **2018**, *9*, 2415.
(14) Chen, B.; Wang, F. Emerging Frontiers of Upconversion Nanoparticles. *Trends Chem.* **2020**, *2*, 427−439.
(15) Kenry; Duan, Y.; Liu, B. Recent Advances of Optical Imaging in the Second Near-Infrared Window. *Adv. Mater.* **2018**, *30*, 1802394.
(16) Hong, G.; Antaris, A. L.; Dai, H. Near-infrared fluorophores for biomedical imaging. *Nat. Biomed. Eng.* **2017**, *1*, 0010.
(17) Fan, Y.; Zhang, F. A New Generation of NIR-II Probes: Lanthanide-Based Nanocrystals for Bioimaging and Biosensing. *Adv. Opt. Mater.* **2019**, *7*, 1801417.
(18) Zhu, X.; Zhang, J.; Liu, J.; Zhang, Y. Recent Progress of Rare-Earth Doped Upconversion Nanoparticles: Synthesis, Optimization, and Applications. *Adv. Sci.* **2019**, *6*, 1901358.
(19) Gai, S.; Yang, G.; Yang, P.; He, F.; Lin, J.; Jin, D.; Xing, B. Recent advances in functional nanomaterials for light−triggered cancer therapy. *Nano Today* **2018**, *19*, 146−187.
(20) Gu, B.; Zhang, Q. Recent Advances on Functionalized Upconversion Nanoparticles for Detection of Small Molecules and Ions in Biosystems. *Adv. Sci.* **2018**, *5*, 1700609.
(21) Li, H.; Wang, X.; Huang, D.; Chen, G. Recent advances of lanthanide-doped upconversion nanoparticles for biological applications. *Nanotechnology* **2020**, *31*, 072001.
(22) Song, C.; Zhang, S.; Zhou, Q.; Hai, H.; Zhao, D.; Hui, Y. Upconversion nanoparticles for bioimaging. *Nanotechnol. Rev.* **2017**, *6*, 233.
(23) Zhou, J.; Liu, Q.; Feng, W.; Sun, Y.; Li, F. Upconversion Luminescent Materials: Advances and Applications. *Chem. Rev.* **2015**, *115*, 395−465.
(24) Deisseroth, K. Optogenetics: 10 years of microbial opsins in neuroscience. *Nat. Neurosci.* **2015**, *18*, 1213−1225.
(25) Zhang, K.; Cui, B. Optogenetic control of intracellular signaling pathways. *Trends Biotechnol.* **2015**, *33*, 92−100.
(26) Zhang, F.; Vierock, J.; Yizhar, O.; Fenno, L. E.; Tsunoda, S.; Kianianmomeni, A.; Prigge, M.; Berndt, A.; Cushman, J.; Polle, J.; Magnuson, J.; Hegemann, P.; Deisseroth, K. The Microbial Opsin Family of Optogenetic Tools. *Cell* **2011**, *147*, 1446−1457.
(27) Warden, M. R.; Cardin, J. A.; Deisseroth, K. Optical Neural Interfaces. *Annu. Rev. Biomed. Eng.* **2014**, *16*, 103−129.
(28) Wang, Z.; Hu, M.; Ai, X.; Zhang, Z.; Xing, B. Near-Infrared Manipulation of Membrane Ion Channels via Upconversion Optogenetics. *Adv. Biosyst.* **2019**, *3*, 1800233.
(29) Wang, Y.; Lin, X.; Chen, X.; Chen, X.; Xu, Z.; Zhang, W.; Liao, Q.; Duan, X.; Wang, X.; Liu, M.; Wang, F.; He, J.; Shi, P. Tetherless near-infrared control of brain activity in behaving animals using fully implantable upconversion microdevices. *Biomaterials* **2017**, *142*, 136−148.
(30) Ding, H.; Lu, L.; Shi, Z.; Wang, D.; Li, L.; Li, X.; Ren, Y.; Liu, C.; Cheng, D.; Kim, H.; Giebink, N. C.; Wang, X.; Yin, L.; Zhao, L.; Luo, M.; Sheng, X. Microscale optoelectronic infrared-to-visible upconversion devices and their use as injectable light sources. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, 6632.
(31) Lin, X.; Chen, X.; Zhang, W.; Sun, T.; Fang, P.; Liao, Q.; Chen, X.; He, J.; Liu, M.; Wang, F.; Shi, P. Core−Shell−Shell Upconversion Nanoparticles with Enhanced Emission for Wireless Optogenetic Inhibition. *Nano Lett.* **2018**, *18*, 948−956.
(32) Wang, Y.; Xie, K.; Yue, H.; Chen, X.; Luo, X.; Liao, Q.; Liu, M.; Wang, F.; Shi, P. Flexible and fully implantable upconversion device for wireless optogenetic stimulation of the spinal cord in behaving animals. *Nanoscale* **2020**, *12*, 2406−2414.
(33) Shah, S.; Liu, J.-J.; Pasquale, N.; Lai, J.; McGowan, H.; Pang, Z. P.; Lee, K.-B. Hybrid upconversion nanomaterials for optogenetic neuronal control. *Nanoscale* **2015**, *7*, 16571−16577.
(34) Hososhima, S.; Yuasa, H.; Ishizuka, T.; Hoque, M. R.; Yamashita, T.; Yamanaka, A.; Sugano, E.; Tomita, H.; Yawo, H. Near-infrared (NIR) up-conversion optogenetics. *Sci. Rep.* **2015**, *5*, 16533.
(35) Wu, X.; Zhang, Y.; Takle, K.; Bilsel, O.; Li, Z.; Lee, H.; Zhang, Z.; Li, D.; Fan, W.; Duan, C.; Chan, E. M.; Lois, C.; Xiang, Y.; Han, G. Dye-Sensitized Core/Active Shell Upconversion Nanoparticles for Optogenetics and Bioimaging Applications. *ACS Nano* **2016**, *10*, 1060−1066.
(36) Bansal, A.; Liu, H.; Jayakumar, M. K. G.; Andersson-Engels, S.; Zhang, Y. Quasi-Continuous Wave Near-Infrared Excitation of Upconversion Nanoparticles for Optogenetic Manipulation of C. elegans. *Small* **2016**, *12*, 1732−1743.
(37) Chen, S.; Weitemier, A. Z.; Zeng, X.; He, L.; Wang, X.; Tao, Y.; Huang, A. J. Y.; Hashimotodani, Y.; Kano, M.; Iwasaki, H.; Parajuli, L. K.; Okabe, S.; Teh, D. B. L.; All, A. H.; Tsutsui-Kimura, I.; Tanaka, K. F.; Liu, X.; McHugh, T. J. Near-infrared deep brain stimulation via upconversion nanoparticle−mediated optogenetics. *Science* **2018**, *359*, 679.
(38) Miyazaki, T.; Chowdhury, S.; Yamashita, T.; Matsubara, T.; Yawo, H.; Yuasa, H.; Yamanaka, A. Large Timescale Interrogation of Neuronal Function by Fiberless Optogenetics Using Lanthanide Micro-particles. *Cell Rep.* **2019**, *26*, 1033−1043.
(39) He, L.; Zhang, Y.; Ma, G.; Tan, P.; Li, Z.; Zang, S.; Wu, X.; Jing, J.; Fang, S.; Zhou, L.; Wang, Y.; Huang, Y.; Hogan, P. G.; Han, G.; Zhou, Y. Near-infrared photoactivatable control of Ca2+ signaling and optogenetic immunomodulation. *eLife* **2015**, *4*, No. e10024.
(40) Ai, X.; Lyu, L.; Zhang, Y.; Tang, Y.; Mu, J.; Liu, F.; Zhou, Y.; Zuo, Z.; Liu, G.; Xing, B. Remote Regulation of Membrane Channel Activity by Site-Specific Localization of Lanthanide-Doped Upconversion Nanocrystals. *Angew. Chem., Int. Ed.* **2017**, *56*, 3031−3035.
(41) Mei, Q.; Bansal, A.; Jayakumar, M. K. G.; Zhang, Z.; Zhang, J.; Huang, H.; Yu, D.; Ramachandra, C. J. A.; Hausenloy, D. J.; Soong, T. W.; Zhang, Y. Manipulating energy migration within single lanthanide activator for switchable upconversion emissions towards bidirectional photoactivation. *Nat. Commun.* **2019**, *10*, 4416.
(42) Zheng, B.; Wang, H.; Pan, H.; Liang, C.; Ji, W.; Zhao, L.; Chen, H.; Gong, X.; Wu, X.; Chang, J. Near-Infrared Light Triggered Upconversion Optogenetic Nanosystem for Cancer Therapy. *ACS Nano* **2017**, *11*, 11898−11907.
(43) Pan, H.; Wang, H.; Yu, J.; Huang, X.; Hao, Y.; Zhang, C.; Ji, W.; Yang, M.; Gong, X.; Wu, X.; Chang, J. Near-infrared light remotely up-regulate autophagy with spatiotemporal precision via upconversion optogenetic nanosystem. *Biomaterials* **2019**, *199*, 22−31.
(44) Zhong, Y.; Ma, Z.; Zhu, S.; Yue, J.; Zhang, M.; Antaris, A. L.; Yuan, J.; Cui, R.; Wan, H.; Zhou, Y.; Wang, W.; Huang, N. F.; Luo, J.;

https://dx.doi.org/10.1021/acsmaterialslett.0c00377
ACS Materials Lett. 2020, 2, 1516−1531

Hu, Z.; Dai, H. Boosting the down-shifting luminescence of rare-earth nanocrystals for biological imaging beyond 1500 nm. *Nat. Commun.* **2017**, *8*, 737.
(45) Ren, F.; Ding, L.; Liu, H.; Huang, Q.; Zhang, H.; Zhang, L.; Zeng, J.; Sun, Q.; Li, Z.; Gao, M. Ultra-small nanocluster mediated synthesis of Nd3+-doped core-shell nanocrystals with emission in the second near-infrared window for multimodal imaging of tumor vasculature. *Biomaterials* **2018**, *175*, 30−43.
(46) Peng, P.; Wu, N.; Ye, L.; Jiang, F.; Feng, W.; Li, F.; Liu, Y.; Hong, M. Biodegradable Inorganic Upconversion Nanocrystals for *In Vivo* Applications. *ACS Nano* **2020**, DOI: 10.1021/acsnano.0c02601.
(47) Drees, C.; Raj, A. N.; Kurre, R.; Busch, K. B.; Haase, M.; Piehler, J. Engineered Upconversion Nanoparticles for Resolving Protein Interactions inside Living Cells. *Angew. Chem., Int. Ed.* **2016**, *55*, 11668−11672.
(48) Zeng, X.; Chen, S.; Weitemier, A.; Han, S.; Blasiak, A.; Prasad, A.; Zheng, K.; Yi, Z.; Luo, B.; Yang, I.-H.; Thakor, N.; Chai, C.; Lim, K.-L.; McHugh, T. J.; All, A. H.; Liu, X. Visualization of Intra-neuronal Motor Protein Transport through Upconversion Microscopy. *Angew. Chem., Int. Ed.* **2019**, *58*, 9262−9268.
(49) Wang, F.; Wen, S.; He, H.; Wang, B.; Zhou, Z.; Shimoni, O.; Jin, D. Microscopic inspection and tracking of single upconversion nanoparticles in living cells. *Light: Sci. Appl.* **2018**, *7*, 18007−18007.
(50) Chen, C.; Wang, F.; Wen, S.; Su, Q. P.; Wu, M. C. L.; Liu, Y.; Wang, B.; Li, D.; Shan, X.; Kianinia, M.; Aharonovich, I.; Toth, M.; Jackson, S. P.; Xi, P.; Jin, D. Multi-photon near-infrared emission saturation nanoscopy using upconversion nanoparticles. *Nat. Commun.* **2018**, *9*, 3290.
(51) Ma, Y.; Bao, J.; Zhang, Y.; Li, Z.; Zhou, X.; Wan, C.; Huang, L.; Zhao, Y.; Han, G.; Xue, T. Mammalian Near-Infrared Image Vision through Injectable and Self-Powered Retinal Nanoantennae. *Cell* **2019**, *177*, 243−255.
(52) Diao, S.; Hong, G.; Antaris, A. L.; Blackburn, J. L.; Cheng, K.; Cheng, Z.; Dai, H. Biological imaging without autofluorescence in the second near-infrared region. *Nano Res.* **2015**, *8*, 3027−3034.
(53) Tsukasaki, Y.; Komatsuzaki, A.; Mori, Y.; Ma, Q.; Yoshioka, Y.; Jin, T. A short-wavelength infrared emitting multimodal probe for non-invasive visualization of phagocyte cell migration in living mice. *Chem. Commun.* **2014**, *50*, 14356−14359.
(54) Xue, Z.; Zeng, S.; Hao, J. Non-invasive through-skull brain vascular imaging and small tumor diagnosis based on NIR-II emissive lanthanide nanoprobes beyond 1500 nm. *Biomaterials* **2018**, *171*, 153−163.
(55) Zhao, M.; Li, B.; Wang, P.; Lu, L.; Zhang, Z.; Liu, L.; Wang, S.; Li, D.; Wang, R.; Zhang, F. Supramolecularly Engineered NIR-II and Upconversion Nanoparticles *In Vivo* Assembly and Disassembly to Improve Bioimaging. *Adv. Mater.* **2018**, *30*, 1804982.
(56) Zhong, Y.; Ma, Z.; Wang, F.; Wang, X.; Yang, Y.; Liu, Y.; Zhao, X.; Li, J.; Du, H.; Zhang, M.; Cui, Q.; Zhu, S.; Sun, Q.; Wan, H.; Tian, Y.; Liu, Q.; Wang, W.; Garcia, K. C.; Dai, H. *In vivo* molecular imaging for immunotherapy using ultra-bright near-infrared-IIb rare-earth nanoparticles. *Nat. Biotechnol.* **2019**, *37*, 1322−1331.
(57) Wang, P.; Fan, Y.; Lu, L.; Liu, L.; Fan, L.; Zhao, M.; Xie, Y.; Xu, C.; Zhang, F. NIR-II nanoprobes in-vivo assembly to improve image-guided surgery for metastatic ovarian cancer. *Nat. Commun.* **2018**, *9*, 2898.
(58) Zhang, H.; Fan, Y.; Pei, P.; Sun, C.; Lu, L.; Zhang, F. Tm3+-Sensitized NIR-II Fluorescent Nanocrystals for *In Vivo* Information Storage and Decoding. *Angew. Chem., Int. Ed.* **2019**, *58*, 10153−10157.
(59) Gu, Y.; Guo, Z.; Yuan, W.; Kong, M.; Liu, Y.; Liu, Y.; Gao, Y.; Feng, W.; Wang, F.; Zhou, J.; Jin, D.; Li, F. High-sensitivity imaging of time-domain near-infrared light transducer. *Nat. Photonics* **2019**, *13*, 525−531.
(60) Peng, J.; Xu, W.; Teoh, C. L.; Han, S.; Kim, B.; Samanta, A.; Er, J. C.; Wang, L.; Yuan, L.; Liu, X.; Chang, Y.-T. High-Efficiency *in Vitro* and *in Vivo* Detection of Zn2+ by Dye-Assembled Upconversion Nanoparticles. *J. Am. Chem. Soc.* **2015**, *137*, 2336−2342.
(61) Liu, J.; Pan, L.; Shang, C.; Lu, B.; Wu, R.; Feng, Y.; Chen, W.; Zhang, R.; Bu, J.; Xiong, Z.; Bu, W.; Du, J.; Shi, J. A highly sensitive and selective nanosensor for near-infrared potassium imaging. *Sci. Adv.* **2020**, *6*, eaax9757.
(62) Peng, J.; Teoh, C. L.; Zeng, X.; Samanta, A.; Wang, L.; Xu, W.; Su, D.; Yuan, L.; Liu, X.; Chang, Y.-T. Development of a Highly Selective, Sensitive, and Fast Response Upconversion Luminescent Platform for Hydrogen Sulfide Detection. *Adv. Funct. Mater.* **2016**, *26*, 191−199.
(63) Liu, Y.; Jia, Q.; Zhai, X.; Mao, F.; Jiang, A.; Zhou, J. Rationally designed pure-inorganic upconversion nanoprobes for ultra-highly selective hydrogen sulfide imaging and elimination *in vivo*. *Chem. Sci.* **2019**, *10*, 1193−1200.
(64) Lei, X.; Li, R.; Tu, D.; Shang, X.; Liu, Y.; You, W.; Sun, C.; Zhang, F.; Chen, X. Intense near-infrared-II luminescence from NaCeF4:Er/Yb nanoprobes for *in vitro* bioassay and *in vivo* bioimaging. *Chem. Sci.* **2018**, *9*, 4682−4688.
(65) Rabie, H.; Zhang, Y.; Pasquale, N.; Lagos, M. J.; Batson, P. E.; Lee, K.-B. NIR Biosensing of Neurotransmitters in Stem Cell-Derived Neural Interface Using Advanced Core−Shell Upconversion Nanoparticles. *Adv. Mater.* **2019**, *31*, 1806991.
(66) Nathan, C.; Cunningham-Bussel, A. Beyond oxidative stress: an immunologist's guide to reactive oxygen species. *Nat. Rev. Immunol.* **2013**, *13*, 349−361.
(67) Hao, C.; Wu, X.; Sun, M.; Zhang, H.; Yuan, A.; Xu, L.; Xu, C.; Kuang, H. Chiral Core−Shell Upconversion Nanoparticle@MOF Nanoassemblies for Quantification and Bioimaging of Reactive Oxygen Species *in Vivo*. *J. Am. Chem. Soc.* **2019**, *141*, 19373−19378.
(68) Liu, L.; Wang, S.; Zhao, B.; Pei, P.; Fan, Y.; Li, X.; Zhang, F. Er3+ Sensitized 1530 nm to 1180 nm Second Near-Infrared Window Upconversion Nanocrystals for *In Vivo* Biosensing. *Angew. Chem., Int. Ed.* **2018**, *57*, 7518−7522.
(69) Peng, J.; Samanta, A.; Zeng, X.; Han, S.; Wang, L.; Su, D.; Loong, D. T. B.; Kang, N.-Y.; Park, S.-J.; All, A. H.; Jiang, W.; Yuan, L.; Liu, X.; Chang, Y.-T. Real-Time *In Vivo* Hepatotoxicity Monitoring through Chromophore-Conjugated Photon-Upconverting Nanoprobes. *Angew. Chem., Int. Ed.* **2017**, *56*, 4165−4169.
(70) Zhao, M.; Li, B.; Wu, Y.; He, H.; Zhu, X.; Zhang, H.; Dou, C.; Feng, L.; Fan, Y.; Zhang, F. A Tumor-Microenvironment-Responsive Lanthanide−Cyanine FRET Sensor for NIR-II Luminescence-Lifetime *In Situ* Imaging of Hepatocellular Carcinoma. *Adv. Mater.* **2020**, *32*, 2001172.
(71) Ai, X.; Wang, Z.; Cheong, H.; Wang, Y.; Zhang, R.; Lin, J.; Zheng, Y.; Gao, M.; Xing, B. Multispectral optoacoustic imaging of dynamic redox correlation and pathophysiological progression utilizing upconversion nanoprobes. *Nat. Commun.* **2019**, *10*, 1087.
(72) Li, S.; Xu, L.; Sun, M.; Wu, X.; Liu, L.; Kuang, H.; Xu, C. Hybrid Nanoparticle Pyramids for Intracellular Dual MicroRNAs Biosensing and Bioimaging. *Adv. Mater.* **2017**, *29*, 1606086.
(73) Zhang, K.; Yang, L.; Lu, F.; Wu, X.; Zhu, J. J. A Universal Upconversion Sensing Platform for the Sensitive Detection of Tumour-Related ncRNA through an Exo III-Assisted Cycling Amplification Strategy. *Small* **2018**, *14*, 1703858.
(74) Chu, H.; Zhao, J.; Mi, Y.; Zhao, Y.; Li, L. Near-Infrared Light-Initiated Hybridization Chain Reaction for Spatially and Temporally Resolved Signal Amplification. *Angew. Chem., Int. Ed.* **2019**, *58*, 14877−14881.
(75) Qu, A.; Sun, M.; Xu, L.; Hao, C.; Wu, X.; Xu, C.; Kotov, N. A.; Kuang, H. Quantitative zeptomolar imaging of miRNA cancer markers with nanoparticle assemblies. *Proc. Natl. Acad. Sci. U. S. A.* **2019**, *116*, 3391.
(76) Song, X.; Li, S.; Guo, H.; You, W.; Shang, X.; Li, R.; Tu, D.; Zheng, W.; Chen, Z.; Yang, H.; Chen, X. Graphene-Oxide-Modified Lanthanide Nanoprobes for Tumor-Targeted Visible/NIR-II Luminescence Imaging. *Angew. Chem., Int. Ed.* **2019**, *58*, 18981−18986.
(77) Li, Y.; Jia, D.; Ren, W.; Shi, F.; Liu, C. A Versatile Photoinduced Electron Transfer-Based Upconversion Fluorescent Biosensing Platform for the Detection of Disease Biomarkers and Nerve Agent. *Adv. Funct. Mater.* **2019**, *29*, 1903191.
(78) Zhou, L.; Fan, Y.; Wang, R.; Li, X.; Fan, L.; Zhang, F. High-Capacity Upconversion Wavelength and Lifetime Binary Encoding for

Multiplexed Biodetection. *Angew. Chem., Int. Ed.* **2018**, *57*, 12824−12829.
(79) Su, Q.; Feng, W.; Yang, D.; Li, F. Resonance Energy Transfer in Upconversion Nanoplatforms for Selective Biodetection. *Acc. Chem. Res.* **2017**, *50*, 32−40.
(80) Yang, Y.; Aw, J.; Xing, B. Nanostructures for NIR light-controlled therapies. *Nanoscale* **2017**, *9*, 3698−3718.
(81) Huang, L.; Li, Z.; Zhao, Y.; Zhang, Y.; Wu, S.; Zhao, J.; Han, G. Ultralow-Power Near Infrared Lamp Light Operable Targeted Organic Nanoparticle Photodynamic Therapy. *J. Am. Chem. Soc.* **2016**, *138*, 14586−14591.
(82) Yao, C.; Wang, P.; Li, X.; Hu, X.; Hou, J.; Wang, L.; Zhang, F. Near-Infrared-Triggered Azobenzene-Liposome/Upconversion Nanoparticle Hybrid Vesicles for Remotely Controlled Drug Delivery to Overcome Cancer Multidrug Resistance. *Adv. Mater.* **2016**, *28*, 9341−9348.
(83) Han, S.; Samanta, A.; Xie, X.; Huang, L.; Peng, J.; Park, S. J.; Teh, D. B. L.; Choi, Y.; Chang, Y.-T.; All, A. H.; Yang, Y.; Xing, B.; Liu, X. Gold and Hairpin DNA Functionalization of Upconversion Nanocrystals for Imaging and *In Vivo* Drug Delivery. *Adv. Mater.* **2017**, *29*, 1700244.
(84) Li, Y.; Di, Z.; Gao, J.; Cheng, P.; Di, C.; Zhang, G.; Liu, B.; Shi, X.; Sun, L.-D.; Li, L.; Yan, C.-H. Heterodimers Made of Upconversion Nanoparticles and Metal−Organic Frameworks. *J. Am. Chem. Soc.* **2017**, *139*, 13804−13810.
(85) Xu, J.; Yang, P.; Sun, M.; Bi, H.; Liu, B.; Yang, D.; Gai, S.; He, F.; Lin, J. Highly Emissive Dye-Sensitized Upconversion Nanostructure for Dual-Photosensitizer Photodynamic Therapy and Bioimaging. *ACS Nano* **2017**, *11*, 4133−4144.
(86) Ai, X.; Ho, C. J. H.; Aw, J.; Attia, A. B. E.; Mu, J.; Wang, Y.; Wang, X.; Wang, Y.; Liu, X.; Chen, H.; Gao, M.; Chen, X.; Yeow, E. K. L.; Liu, G.; Olivo, M.; Xing, B. *In vivo* covalent cross-linking of photon-converted rare-earth nanostructures for tumour localization and theranostics. *Nat. Commun.* **2016**, *7*, 10432.
(87) Liu, C.; Liu, B.; Zhao, J.; Di, Z.; Chen, D.; Gu, Z.; Li, L.; Zhao, Y. Nd3+-Sensitized Upconversion Metal−Organic Frameworks for Mitochondria-Targeted Amplified Photodynamic Therapy. *Angew. Chem., Int. Ed.* **2020**, *59*, 2634−2638.
(88) Mi, Y.; Cheng, H.-B.; Chu, H.; Zhao, J.; Yu, M.; Gu, Z.; Zhao, Y.; Li, L. A photochromic upconversion nanoarchitecture: towards activatable bioimaging and dual NIR light-programmed singlet oxygen generation. *Chem. Sci.* **2019**, *10*, 10231−10239.
(89) Zhang, Z.; Jayakumar, M. K. G.; Zheng, X.; Shikha, S.; Zhang, Y.; Bansal, A.; Poon, D. J. J.; Chu, P. L.; Yeo, E. L. L.; Chua, M. L. K.; Chee, S. K.; Zhang, Y. Upconversion superballs for programmable photoactivation of therapeutics. *Nat. Commun.* **2019**, *10*, 4586.
(90) Chu, H.; Zhao, J.; Mi, Y.; Di, Z.; Li, L. NIR-light-mediated spatially selective triggering of anti-tumor immunity via upconversion nanoparticle-based immunodevices. *Nat. Commun.* **2019**, *10*, 2839.
(91) Qu, A.; Wu, X.; Li, S.; Sun, M.; Xu, L.; Kuang, H.; Xu, C. An NIR-Responsive DNA-Mediated Nanotetrahedron Enhances the Clearance of Senescent Cells. *Adv. Mater.* **2020**, *32*, 2000184.
(92) Ding, B.; Shao, S.; Yu, C.; Teng, B.; Wang, M.; Cheng, Z.; Wong, K.-L.; Ma, P. a.; Lin, J. Large-Pore Mesoporous-Silica-Coated Upconversion Nanoparticles as Multifunctional Immunoadjuvants with Ultrahigh Photosensitizer and Antigen Loading Efficiency for Improved Cancer Photodynamic Immunotherapy. *Adv. Mater.* **2018**, *30*, 1802479.
(93) Zhu, X.; Li, J.; Qiu, X.; Liu, Y.; Feng, W.; Li, F. Upconversion nanocomposite for programming combination cancer therapy by precise control of microscopic temperature. *Nat. Commun.* **2018**, *9*, 2176.
(94) Yan, S.; Zeng, X.; Tang, Y. a.; Liu, B.-F.; Wang, Y.; Liu, X. Activating Antitumor Immunity and Antimetastatic Effect Through Polydopamine-Encapsulated Core−Shell Upconversion Nanoparticles. *Adv. Mater.* **2019**, *31*, 1905825.
(95) Grüner, M. C.; Arai, M. S.; Carreira, M.; Inada, N.; de Camargo, A. S. S. Functionalizing the Mesoporous Silica Shell of Upconversion Nanoparticles To Enhance Bacterial Targeting and Killing via Photosensitizer-Induced Antimicrobial Photodynamic Therapy. *ACS Appl. Bio Mater.* **2018**, *1*, 1028−1036.
(96) Liu, J.; Yu, M.; Zeng, G.; Cao, J.; Wang, Y.; Ding, T.; Yang, X.; Sun, K.; Parvizi, J.; Tian, S. Dual antibacterial behavior of a curcumin−upconversion photodynamic nanosystem for efficient eradication of drug-resistant bacteria in a deep joint infection. *J. Mater. Chem. B* **2018**, *6*, 7854−7861.
(97) Xu, F.; Zhao, Y.; Hu, M.; Zhang, P.; Kong, N.; Liu, R.; Liu, C.; Choi, S. K. Lanthanide-doped core-shell nanoparticles as a multimodality platform for imaging and photodynamic therapy. *Chem. Commun.* **2018**, *54*, 9525−9528.
(98) Zhang, Y.; Huang, P.; Wang, D.; Chen, J.; Liu, W.; Hu, P.; Huang, M.; Chen, X.; Chen, Z. Near-infrared-triggered antibacterial and antifungal photodynamic therapy based on lanthanide-doped upconversion nanoparticles. *Nanoscale* **2018**, *10*, 15485−15495.
(99) Liu, W.; Zhang, Y.; You, W.; Su, J.; Yu, S.; Dai, T.; Huang, Y.; Chen, X.; Song, X.; Chen, Z. Near-infrared-excited upconversion photodynamic therapy of extensively drug-resistant Acinetobacter baumannii based on lanthanide nanoparticles. *Nanoscale* **2020**, *12*, 13948−13957.
(100) Xu, J.; Liu, N.; Wu, D.; Gao, Z.; Song, Y. Y.; Schmuki, P. Upconversion Nanoparticle-Assisted Payload Delivery from TiO2 under Near-Infrared Light Irradiation for Bacterial Inactivation. *ACS Nano* **2020**, *14*, 337−346.
(101) Yang, Y.; Shao, Q.; Deng, R.; Wang, C.; Teng, X.; Cheng, K.; Cheng, Z.; Huang, L.; Liu, Z.; Liu, X.; Xing, B. *In Vitro* and *In Vivo* Uncaging and Bioluminescence Imaging by Using Photocaged Upconversion Nanoparticles. *Angew. Chem., Int. Ed.* **2012**, *51*, 3125−3129.
(102) Min, Y.; Li, J.; Liu, F.; Yeow, E. K. L.; Xing, B. Near-Infrared Light-Mediated Photoactivation of a Platinum Antitumor Prodrug and Simultaneous Cellular Apoptosis Imaging by Upconversion-Luminescent Nanoparticles. *Angew. Chem., Int. Ed.* **2014**, *53*, 1012−1016.
(103) Pan, Y.; Yang, J.; Luan, X.; Liu, X.; Li, X.; Yang, J.; Huang, T.; Sun, L.; Wang, Y.; Lin, Y.; Song, Y. Near-infrared upconversion−activated CRISPR-Cas9 system: A remote-controlled gene editing platform. *Sci. Adv.* **2019**, *5*, eaav7199.
(104) Yan, Z.; Qin, H.; Ren, J.; Qu, X. Photocontrolled Multidirectional Differentiation of Mesenchymal Stem Cells on an Upconversion Substrate. *Angew. Chem., Int. Ed.* **2018**, *57*, 11182−11187.
(105) Li, W.; Liu, Z.; Chen, Z.; Kang, L.; Guan, Y.; Ren, J.; Qu, X. An intelligent near-infrared light activatable nanosystem for accurate regulation of zinc signaling in living cells. *Nano Res.* **2017**, *10*, 3068−3076.
(106) Chen, Z.; Zhou, L.; Bing, W.; Zhang, Z.; Li, Z.; Ren, J.; Qu, X. Light Controlled Reversible Inversion of Nanophosphor-Stabilized Pickering Emulsions for Biphasic Enantioselective Biocatalysis. *J. Am. Chem. Soc.* **2014**, *136*, 7498−7504.
(107) Li, W.; Dong, K.; Wang, H.; Zhang, P.; Sang, Y.; Ren, J.; Qu, X. Remote and reversible control of *in vivo* bacteria clustering by NIR-driven multivalent upconverting nanosystems. *Biomaterials* **2019**, *217*, 119310.
(108) Wu, S.; Blinco, J. P.; Barner-Kowollik, C. Near-Infrared Photoinduced Reactions Assisted by Upconverting Nanoparticles. *Chem. - Eur. J.* **2017**, *23*, 8325−8332.
(109) Wan, W.-L.; Tian, B.; Lin, Y.-J.; Korupalli, C.; Lu, M.-Y.; Cui, Q.; Wan, D.; Chang, Y.; Sung, H.-W. Photosynthesis-inspired H2 generation using a chlorophyll-loaded liposomal nanoplatform to detect and scavenge excess ROS. *Nat. Commun.* **2020**, *11*, 534.
(110) Cong, T. D.; Wang, Z.; Hu, M.; Han, Q.; Xing, B. Extraspecific Manifestation of Nanoheater's Position Effect on Distinctive Cellular Photothermal Responses. *ACS Nano* **2020**, *14*, 5836−5844.
(111) Gnach, A.; Lipinski, T.; Bednarkiewicz, A.; Rybka, J.; Capobianco, J. A. Upconverting nanoparticles: assessing the toxicity. *Chem. Soc. Rev.* **2015**, *44*, 1561−1584.
(112) Sun, Y.; Feng, W.; Yang, P.; Huang, C.; Li, F. The biosafety of lanthanide upconversion nanomaterials. *Chem. Soc. Rev.* **2015**, *44*, 1509−1525.

https://dx.doi.org/10.1021/acsmaterialslett.0c00377
ACS Materials Lett. 2020, 2, 1516−1531

(113) Chen, B.; Wang, F. Combating Concentration Quenching in Upconversion Nanoparticles. *Acc. Chem. Res.* **2020**, *53*, 358−367.
(114) Lyu, L.; Cheong, H.; Ai, X.; Zhang, W.; Li, J.; Yang, H.; Lin, J.; Xing, B. Near-infrared light-mediated rare-earth nanocrystals: recent advances in improving photon conversion and alleviating the thermal effect. *NPG Asia Mater.* **2018**, *10*, 685−702.

https://dx.doi.org/10.1021/acsmaterialslett.0c00377
ACS Materials Lett. 2020, 2, 1516−1531