DOI: 10.1002/((please add manuscript number))
Article type: Progress Report

Nanotransducers for Near-Infrared Photoregulation in Biomedicine

*Jingchao Li, Hongwei Duan and Kanyi Pu**

Dr. J. Li, Prof. H. Duan, Prof. K. Pu
School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore 637457, Singapore
E-mail: kypu@ntu.edu.sg

Keywords: Nanotransducers, photoregulation, near-infrared light, nanoparticles, biomedicine

Abstract. Photoregulation that utilizes light to remotely control biological events provides a precise way to decipher biology and innovate medicine; however, its potential has been limited by the shallow tissue penetration and/or phototoxicity of ultraviolet (UV)/visible light that are required to match the optical responses of endogenous photosensitive substances. Thereby, biologically friendly near-infrared (NIR) light with improved tissue penetration is desired for photoregulation. Since there are few endogenous biomolecules absorbing or emitting light in the NIR region, the development of molecular transducers is essential to convert NIR light into the cues for regulation of biological events. In this regard, optical nanomaterials able to convert NIR light into UV/visible light, heat or free radicals are competent for this task. This progress report summarizes the recent development of optical nanotransducers for NIR light-mediated photoregulation in medicine. The emerging applications including photoregulation of neural activity, gene expression, and visual systems as well as photochemical tissue bonding are highlighted along with the design principles of nanotransducers. Moreover, the current challenges and perspectives in this field are discussed.

1. Introduction

Remote regulation of biological events has played an important role in biology and medicine since it helps disclose underlying physiological processes in living systems and can potentially lead to novel therapeutic modalities.[1-4] Various external stimuli including magnetic fields,[5-8] ultrasounds,[9-11] heating,[12] electric fields,[13-15] and mechanical forces[16-18] have been used as the physical cues to control the specific biological processes at the designated sites of living organisms. These stimulation approaches have enabled regulation of biological activities including gene transfection,[19-21] signaling pathways,[22-24] ion channels,[25-27] protein activities,[28] cell functions,[29-31] molecule separation[32] and tissue regeneration.[33-35] However, magnetic field requires tens to thousands of seconds to induce adequate strength probably due to the slow magnetothermal efficiency and need complicated operation in setting up magnetic equipment;[36] ultrasound has poor tissue targeting and may lead to metastatic disseminations owing to the enhanced vessel permeability;[37] heating and mechanical forces are poorly controllable in both temporal and spatial;[38, 39] and electrical stimulation is invasive and similarly has poor spatial selectivity.[40] Thereby, the limitations of these external stimuli partially hamper their biomedical applications.

One emerging alternative to regulation of biological events is photoregulation, a process in which light is utilized as an external stimulus.[41] Because light has the intrinsic advantages of noninvasiveness, high spatiotemporal resolution, easy controllability over intensity and wavelength,[42] photoregulation holds promising for an abundance of biomedical applications.[43-45] In addition to photothermal therapy (PTT)[46-48] and photodynamic therapy (PDT)[49-51] with the intention of killing disease cells, light-based applications include photothermal opening of ion channels,[52] photo-stimulation of light-sensitive proteins,[53-55] photoactivated uncaging of biomolecules,[56-58] photo-crosslinking of tissues,[59] and photo-controlled delivery of cargos.[60-62] However, photoregulation techniques often encounter certain predicaments that compromise their potential applications.[41, 63] This mainly results

from the widespread use of ultraviolet (UV) or visible light in photoregulation, because the majority of current light-sensitive moieties are only responsive to the light sources at these wavelengths.[63, 64] UV and visible lights have very shallow tissue penetration depth due to their high absorption and scattering in living tissues.[65] In addition, UV light with high energy per photon has a high probability to damage biomolecules (such as nucleic acids, proteins and lipids), potentially leading to phototoxicity.[66] To address these issues, replacement of UV and visible lights with the near-infrared (NIR) light source (700-1000 nm) that has lower tissue absorption, less photon scattering, and deeper tissue penetration are highly desired to achieve photoregulation of different biological events.[67]

Molecular transducers are essential for photoregulation of biological processes because there are few endogenous biomolecules with the ability to response to NIR light.[68] In this regard, optical nanomaterials have shown their potential to be used as advanced nanotransducers to convert light into various forms of cues to trigger biological events or biomolecular activities. For example, upconversion nanoparticles (UCNPs) can convert NIR light into UV and visible lights that match the absorption spectrum of light-sensitive moieties or protein-ion channels.[69-71] Organic semiconducting nanoparticles, nanographene oxide, carbon nanotubes, and metal nanoparticles can convert NIR light to generate local heat to allow photothermal stimulation of temperature-sensitive biological behaviors.[72-75] In addition, upon exposure to NIR light, photosensitizer-based nanostructures are capable of producing reactive oxygen species (ROS), a class of highly reactive molecules, to induce biochemical reactions in living subjects.[76-78]

In this Progress Report, we summarize the recent development of optical nanotransducers for NIR photoregulation applications including photoregulation of neurons, gene expression, and visual systems as well as photochemical tissue bonding (**Figure 1**). In the following, the design principles and optical properties of nanotransducers, and corresponding working mechanisms pertaining to NIR light-mediated photoregulation are discussed along with the

representative examples. At last, a brief summary is given along with the discussion of current challenges and perspectives in this field.

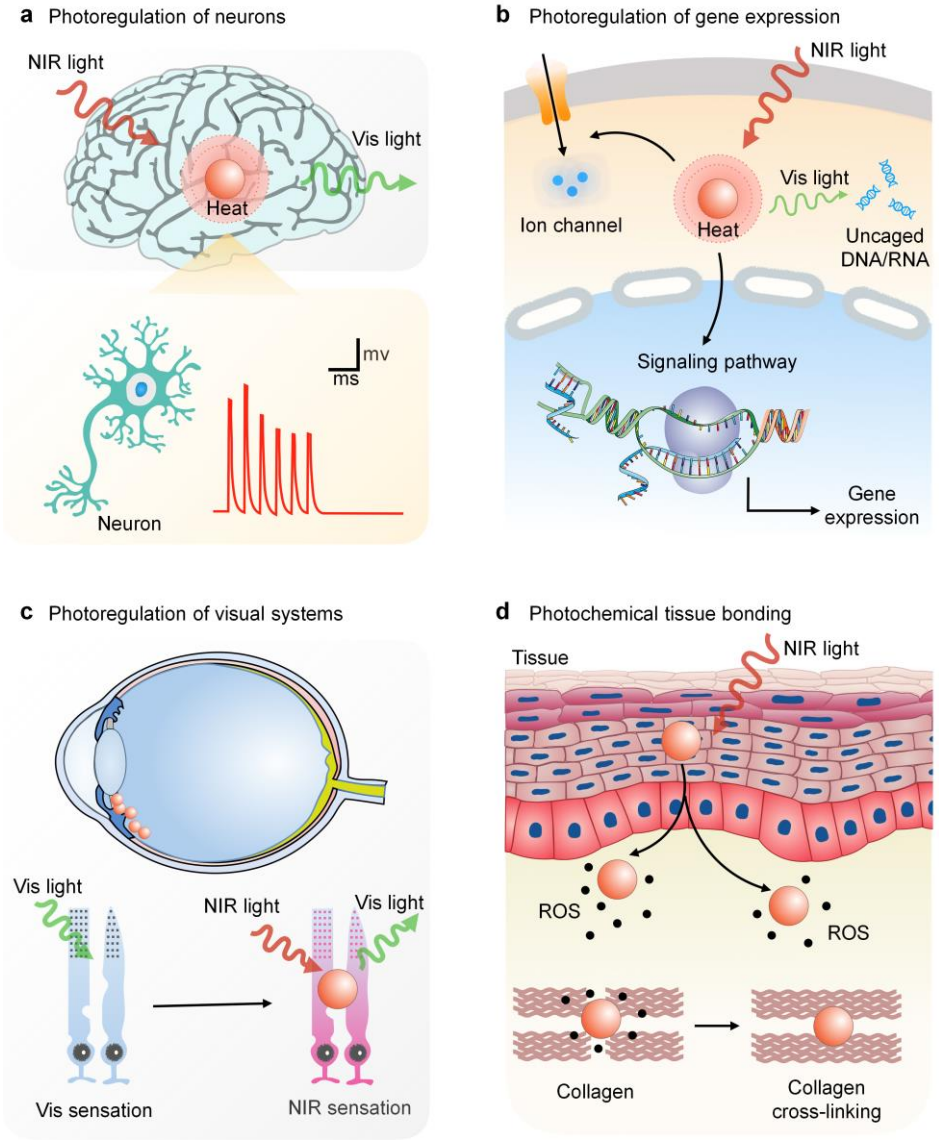


Figure 1. Summary of optical nanotransducers for NIR photoregulation: (a) photoregulation of neurons, (b) photoregulation of gene expression, (c) photoregulation of visual systems, and (d) photochemical tissue bounding.

2. Photoregulation of neurons

Precise regulation of neural activity is crucial for understanding brain functions and can potentially provide new ways to treat neurological diseases.[36, 79, 80] Current techniques for neuron regulation include chemical stimulations, ultrasounds, electric fields, magnetic fields,

local heating and light irradiation.[15] Among them, light has been widely used in neuroscience to allow neuron activations and neuron inhibitions through optogenetics and photothermal stimulation (**Table 1**).

2.1. Optogenetics of neurons

Optogenetics utilizes light to remotely regulate the light-sensitive microbial ion channel proteins of genetically engineered neural cells either *in vitro* or *in vivo*.[81] The microbial ion channel proteins such as channelrhodopsin (ChR), halorhodopsin (NpHR) and archaerhodopsin (Arch) can be stimulated upon exposure to a particular wavelength of light, offering high specificity towards light.[81] With the combinational advantages of genetic techniques and light, optogenetics has emerged as an indispensable modulation strategy in neuroscience.[81] However, current optogenetic methods usually rely on the visible light and thus require the implantation of invasive fiber-optic probes into living tissues for signal stimulation.[82-84] To bypass the shallow tissue penetration issue of existing light-sensitive ion channel proteins, UCNPs with NIR light absorption but visible light emission have been applied in optogenetics.

Utilizations of UCNP-mediated optogenetics for stimulation of cultured neural cells have been widely reported.[85, 86] In a recent study, mouse neuroblastoma/rat dorsal root ganglion (DRG) neuron hybrid ND7/23 cells were genetically engineered to express ChR variants (C1V1 and mVChR1) and then cultured on $NaYF_4$:Sc/Yb/Er UCNP-coated coverslip. Upon NIR laser (975 nm) irradiation, UCNPs emitted green light that subsequently activated C1V1 and mVChR1 to generate action potentials in neural cells.[85] In another similar study, $NaYF_4$:Yb/Tm@$NaYF_4$ core/shell UCNPs were embedded into a biocompatible poly(lactic-co-glycolic acid) (PLGA) film to form a hybrid scaffold for culture of hippocampal neurons expressing ChR2, a microbial ion channel that responded to blue light.[86] Such a UCNPs/PLGA hybrid scaffold allowed conversion of 980 nm NIR light to blue luminescence, inducing the neuronal activation with a comparable efficiency as that of 470 nm blue light. More importantly, the efficiencies of UCNP-mediated optogenetics can be boosted through increasing the

upconversion luminescence of UCNPs. As demonstrated by Han's group, UCNPs were doped with ytterbium ions (Yb^{3+}) into their shells and conjugated with IR-806 dyes to the surface, yielding the dye-sensitized core/active shell UCNPs. Such nanoparticles showed 8- and 1000-fold enhancements in the upconversion efficiency relative to the counterparts without Yb^{3+} doping and without IR-806 dye conjugation, respectively.[87] The amplified upconversion property eventually led to a robust NIR-induced activation of hippocampal neurons expressing ReaChR cultured on the polymer films embedded with the dye-sensitized core/active shell UCNPs.

Thanks to enhanced tissue penetration depths of NIR light, UCNP-mediated optogenetics has been used for stimulation of deep brain neurons in living animals. Incorporation of Tm^{3+} into Yb^{3+}-doped $NaYF_4$ UCNPs allowed the conversion of 980 nm NIR light to blue emission that matched the maximum absorption of ChR2 (**Figure 2**a,b).[88] Blue emission could be recorded in the ventral tegmental area (VTA) of a mouse brain after local injection of UCNPs upon NIR laser irradiation (Figure 2c,d), confirming the upconversion emission in deep brain. Silica-coated UCNPs (termed as $NaYF_4$:Yb/Tm@SiO_2 UCNPs) were chosen for *in vivo* optogenetic activation because of their minimum cytotoxicity (Figure 2e). To test the *in vivo* utility of UCNP-mediated optogenetics, the VTA of tyrosine hydroxylase (TH)-driven Cre recombinase (TH-Cre) transgenic mouse was injected with an adeno-associated virus (AAV) encoding ChR2, leading to Cre-dependent expression of ChR2 in dopamine (DA) neurons (Figure 2f). *In vivo* optogenetic activation of VTA DA neurons was only triggered by NIR light in ChR2-transfected mice with $NaYF_4$:Yb/Tm@SiO_2 UCNPs injection, as indicated by the significantly elevated proportion of neural cells expressing c-Fos, a typical biochemical marker for neuronal activation (Figure 2g). In addition, obvious striatal DA transients were observed in the same treated mice (Figure 2h-j), which reflected the phasic spike activity. Similarly, Wang and Shi et al. reported the utilization of UCNPs for *in vivo* optogenetic activation of rat brain neurons expressing ChR2 and C1V1 by implanting a microoptrode containing Tm^{3+} and

Er^{3+} doped UCNPs into the visual cortex of an adult Sprague-Dawley (SD) rat, respectively.[89] Increased spiking activity and strong expression of c-Fos were observed for neurons after NIR light stimulation.

In addition to neuronal activation, UCNP-mediated optogenetics has permitted inhibition of neurons by stimulating green light sensitive ion channel proteins, such as NpHR and Arch, two commonly used opsin proteins for neuronal inhibition.[90] With co-doping of Er^{3+} and Yb^{3+} into the $NaYF_4$ host lattice, emission of silica-coated UCNPs (termed as $NaYF_4$:Yb/Er@SiO_2 UCNPs) was tuned to ~540 nm that matched the maximum absorption of Arch (Figure 2k).[88] After injection of these UCNPs and NIR laser exposure, mouse with the expression of Arch in the excitatory neurons had an obviously reduced level of c-Fos expression in the granule cells of the dentate gyrus (DS) (Figure 2l,m), indicating effective inhibition of hippocampal neurons. In another study, $NaYF_4$@$NaYF_4$:Yb/Er@$NaYF_4$ core-shell-core structured UCNPs with almost 3-fold enhanced upconversion luminescence at 540-570 nm relative to traditional core-shell counterparts were also developed for optogenetic inhibition of neurons.[91] After implantation of the devices containing these core-shell-core UCNPs into targeted regions deep in the rat brain, electrical activities of NpHR-expressing neurons was reliably inhibited upon NIR laser illumination at 980 nm and could be immediately restored to the normal level by switching off the NIR light. Such a UCNP-mediated optogenetic inhibition was also reported to suppress the secondary motor cortex in behaving mice and modulate their locomotion behaviors in an open field.

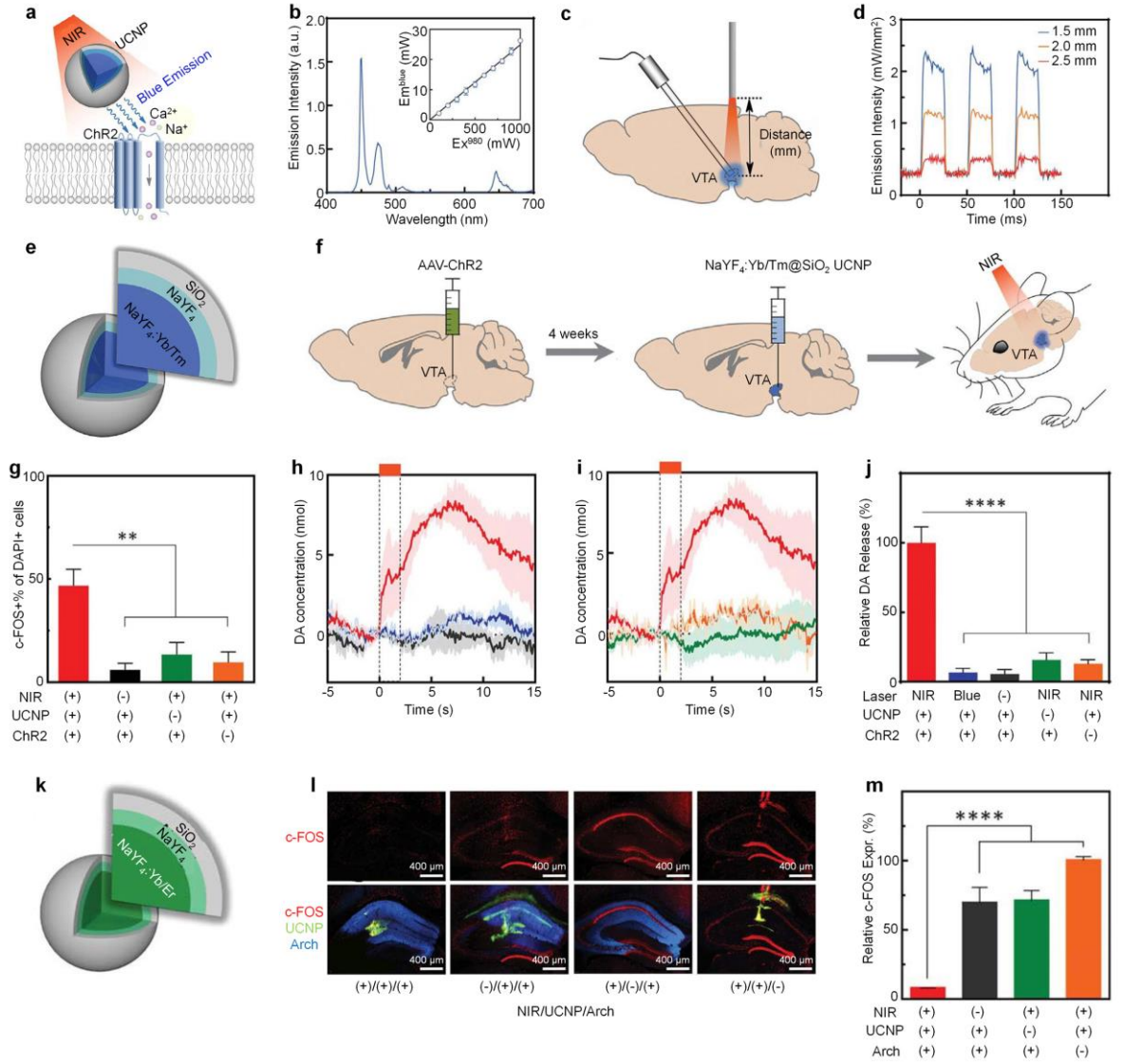


Figure 2. (a) Scheme of UCNP-mediated NIR upconversion optogenetics. (b) Emission spectrum of UCNPs under an excitation at 980 nm. (Inset) Upconversion emission intensity of UCNPs as a function of excitation intensity at 980 nm. (c) Scheme of *in vivo* fiber photometry for measuring UCNP-mediated NIR upconversion in deep brain tissue. The tip of an optic fiber transmitting NIR excitation light was positioned at various distances from the VTA where UCNPs were injected, and their emission was recorded by a second optic fiber. (d) Upconversion emission at the VTA upon 980 nm NIR laser irradiation from varying distances. (e) Scheme of blue-emitting $NaYF_4$:Yb/Tm@SiO_2 UCNPs. (f) *In vivo* experimental scheme for transcranial NIR laser stimulation of VTA in anesthetized mice. (g) Percentage of c-Fos-positive neurons within cell population stained by DAPI (4',6-diamidino-2-phenylindole). (h and i) Transient DA concentrations in the ventral striatum responding to transcranial VTA stimulation under different conditions. Each color refers to a condition shown in (j). (j) The cumulative DA release within 15 s after the start of transcranial stimulation under the five

conditions shown in (h) and (i). (k) Scheme of green-emitting $NaYF_4$:Yb/Er@SiO_2 UCNPs. (l) Confocal fluorescence images of hippocampus following transcranial NIR laser irradiation under four different conditions. (m) c-Fos expression under four different conditions shown in (l). Reprinted with permission.[88] Copyright 2018, American Association for the Advancement of Science.

2.2. Photothermal stimulation

Although optogenetics has achieved successes in regulating neuronal activity, its requirement of complicated genetic modification of target neural cells partially constrains its broad applications.[92] Direct photothermal stimulation of unmodified neurons is an alternative to precisely regulate neuronal activities. In this case, optical nanomaterials can act as photothermal nanotransducers to convert NIR light stimulation into local mild heat (< 43 °C) at the neuronal plasma membrane and such temperature increments allow temperature-sensitive ion channels to be activated, regulating the activities of neurons.

Optical nanomaterials with NIR absorption, including carbon nanohorns (CNHs),[93] gold nanorods (AuNRs),[94-96] and liquid metal nanocapsules,[97] have been shown to be effective in photothermal activation of neurons. Upon interaction with neurons, these optical nanomaterials enabled generation of local mild heat through photothermal conversion under NIR laser irradiation, allowing the activation of temperature-sensitive transient receptor potential cation channel subfamily V member 1 (TRPV1), a typical ion permeable polymodal channel intrinsically overexpressed on the plasma membrane of neurons.[93] The activation of TRPV1 induced Ca^{2+} influx of neurons, a vital biological process in neurotransmitter release. However, without a targeting selectivity and specificity, most of these systems can encounter the predicament of poor activation efficiency and potential damage to the cellular membranes.

To allow selective and specific photothermal activation of neurons, Pu's group designed a semiconducting polymer nanobioconjugate (SPN_{bc}) that targeted TRPV1 receptor on neuron surface.[98] A semiconducting polymer (SP1, **Figure 3**a) was synthesized and transformed into

semiconducting polymer nanoparticles (SPN1) *via* nanocoprecipitation with an amphiphilic polymer, polystyrene-*b*-poly(acrylic acid) (PS-PAA) (Figure 3b). Owing to the enhanced charge transfer of SP1, the maximum absorption of SPN1 was red-shifted by 100 to 766 nm as compared to that of counterpart SPN2 (660 nm), while the control AuNRs had the maximum absorption at 780 nm (Figure 3c). Under 808 nm laser irradiation, SPN1 showed a faster heating capability relative to both SPN2 and AuNRs. SPN1 was conjugated with an anti-TRPV1 antibody to obtain $SPN1_{bc}$, which allowed the effective binding with the TRPV1 ion channels on the surface of ND7/23 neuronal cells (Figure 3d). Such a targeted binding permitted quick diffusion of locally generated heat from $SPN1_{bc}$ to TRPV1, achieving specific activation of TRPV1 ion channels and subsequent intracellular Ca^{2+} influx (Figure 3e). Real-time monitoring of Ca^{2+} influx with a fluorescent turn-on indicator (Fluo-8) showed that as soon as the 808 nm NIR laser irradiation initiated, the Fluo-8 fluorescence immediately increased until its plateau at ~1.5 s for $SPN1_{bc}$-treated ND7/23 cells (Figure 3f,g), while this was not observed for $SPN1_{bc}$-treated TRPV1 negative control cells (HeLa cells) and $SPN2_{bc}$-treated ND7/23 cells. In addition, the TRPV1 Ca^{2+} channels could be reversibly activated and silenced by switching on/off the NIR laser at an interval of 0.5 s (Figure 3h), demonstrating the capability of simultaneous input-output interrogation of neuronal cells within milliseconds.

Nanomaterial-based photothermal stimulation can also be used to inhibit neuronal activity. For example, Nam's group showed that photothermal heating mediated by AuNRs attached on the neural plasma membrane inhibited the action potentials and spike rates of hippocampal neurons upon 785 nm NIR laser exposure, and the neuronal activity was completely recovered after removal of laser source.[99] Such an inhibitory action was reported to be associated with the photothermal stimulation of temperature-sensitive TREK-1 channel, a K^+ channel widely expressed throughout the whole brain region including the hippocampus that intrinsically reduced neuronal activity. The same group also showed that this AuNR-mediated photothermal inhibitory technique could be further integrated into the conventional neurodevices to allow an

effective suppression of the spontaneous firing of hippocampal neurons, and also their signal propagation along neurites evoked by electrical stimulation.[100] Beyond that, gold nanostars (AuNSs) were similarly utilized to optically inhibit neuronal activity even in single cell level.[101]

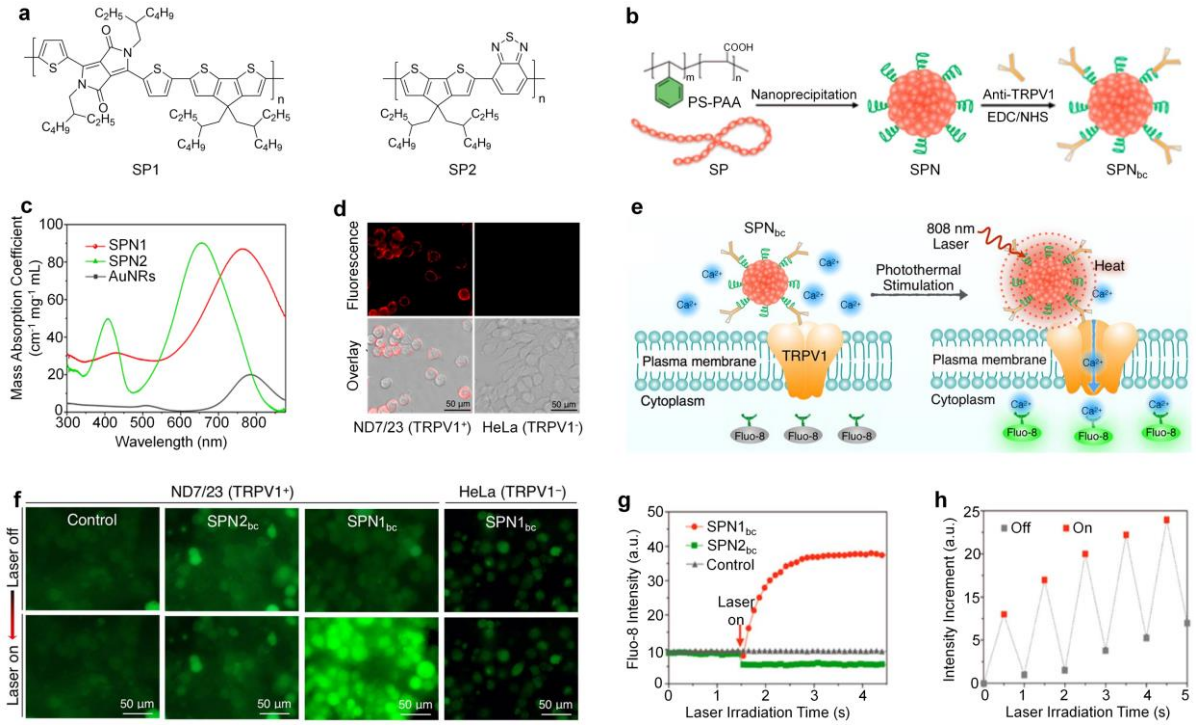


Figure 3. (a) Chemical structures of SP1 and SP2. (b) Schematic illustration of the synthesis of SPN and SPN_{bc}. (c) Absorption of SPN1, SPN2 and AuNRs. (d) Fluorescence cell images of ND7/23 cells and HeLa cells after treatments with $SPN1_{bc}$. (e) Schematic illustration of SPN_{bc} controlled photothermal activation of TRPV1 ion channels in neurons. The intracellular concentration of Ca^{2+} was monitored in real-time using Fluo-8 as the indicator, which turned on its fluorescence upon binding with Ca^{2+}. (f) Fluorescence images of ND7/23 cells or HeLa cells treated with $SPN1_{bc}$ or $SPN2_{bc}$ before and after the laser irradiation at 808 nm for 2 s. (g) The fluorescence intensity of Fluo-8 as a function of the laser irradiation time. (h) Changes in the fluorescence intensity of Fluo-8 with the laser irradiation at 808 nm switching on and off at an interval of 0.5 s. Reprinted with permission.[98] Copyright 2016, American Chemical Society.

3. Photoregulation of gene expression

Remote regulation of intracellular gene expression provides a precise way to understand the physiological roles of a particular gene and its therapeutic potential.[102-104] Currently, radio waves, gas molecules, magnetic fields and light irradiation have been used to remotely switch

on gene expression.[63, 105, 106] Of these, NIR light is the most ideal external trigger because it can precisely control transgenic actions at designated locations and times so as to minimize the off-target gene expression. NIR light-mediated regulations of gene expression can mainly be achieved through three different mechanisms: optogenetics, photothermic gene expression and activation of photocaged transgenic systems (Table 1).

3.1. Optogenetics of gene expression

In addition to neural activity regulation, optogenetics can be adopted to modulate intracellular gene expression.[107] For instance, a NIR-inducible optogenetic nanoplatform (termed as Opto-CRAC) was constructed to enable remote photoregulation of intracellular Ca^{2+} influx and Ca^{2+}-dependent gene expression.[107] In their system, target cells were genetically encoded to express $ORAI1^{StrepTag}$ (streptavidin-binding tag inserted into the second extracellular loop of ORAI1 Ca^{2+} channel) and LOVSoc (stromal interaction molecule 1 cytosolic domain, STIM1-CT fragments inserted with a photoswitch LOV2 domain), while $NaYF_4$:Yb,Tm@$NaYF_4$ UCNPs with a bright blue emission upon 980 nm NIR laser irradiation were conjugated with streptavidin to allow their targeted accumulation onto the plasma membranes (**Figure 4**a). UCNP-transduced blue light well matched the absorption window of LOV2 domains for activation, leading to the opening of ORAI1 Ca^{2+} channels. Thus, Ca^{2+} influx occurred to trigger the gene transcription of Ca^{2+}-dependent master transcriptional regulator NFAT (nuclear factor of activated T cells) and downstream cloned genes of interest, such as luciferase (Figure 4b,c). Interestingly, this optogenetic system was used for activation of dendritic cells (DC)-mediated immunotherapy, wherein NIR light irradiation resulted in a 2-8 fold increment in the expression of MHC-I/II (major histocompatibility complex-I/II), CD86 (cluster of differentiation 86) and CCR7 (CC-chemokine receptor 7) on the surface of DCs (Figure 4d). After the injection of UCNPs-Stv in alliance with ovalbumin (OVA) loaded Opto-CRAC DCs into the B16-OVA murine model of melanoma, an anti-tumor immune response was elicited upon 980 nm NIR

laser irradiation, which significantly suppressed tumor growth and reduced the numbers of tumor metastasis in lungs (Figure 4e-g).

In another study, the use of UCNP-mediated optogenetics to activate apoptotic signaling pathway for cancer therapy was reported.[108] Cancer cells were transfected with DNA plasmids to express blue light responsive Arabidopsis flavoprotein cryptochrome 2 (Cry2), mCherry and Fas-associated protein with death domain (FADD) on their cytoplasmic membranes, while Fas and Cry2 binding partner (Cib1) on the plasma membranes. Under 980 nm NIR laser irradiation, UCNPs emitted local blue light to trigger the translocation of Cry2-mCherry-FADD from cytoplasmic membranes to plasma membranes, inducing the Cry2-Cib1 interaction (Figure 4h,i). At the same time, Fas worked together with its adaptor molecule FADD, which activated the apoptotic signaling pathway (Figure 4j). As a result, such a NIR-controlled optogenetic nanosystem was reported to induce a more than 6-fold enhanced mortality for cancer cells, and significantly suppress tumor growth in living mice, which was impossible for blue light owing to its weak penetrability.

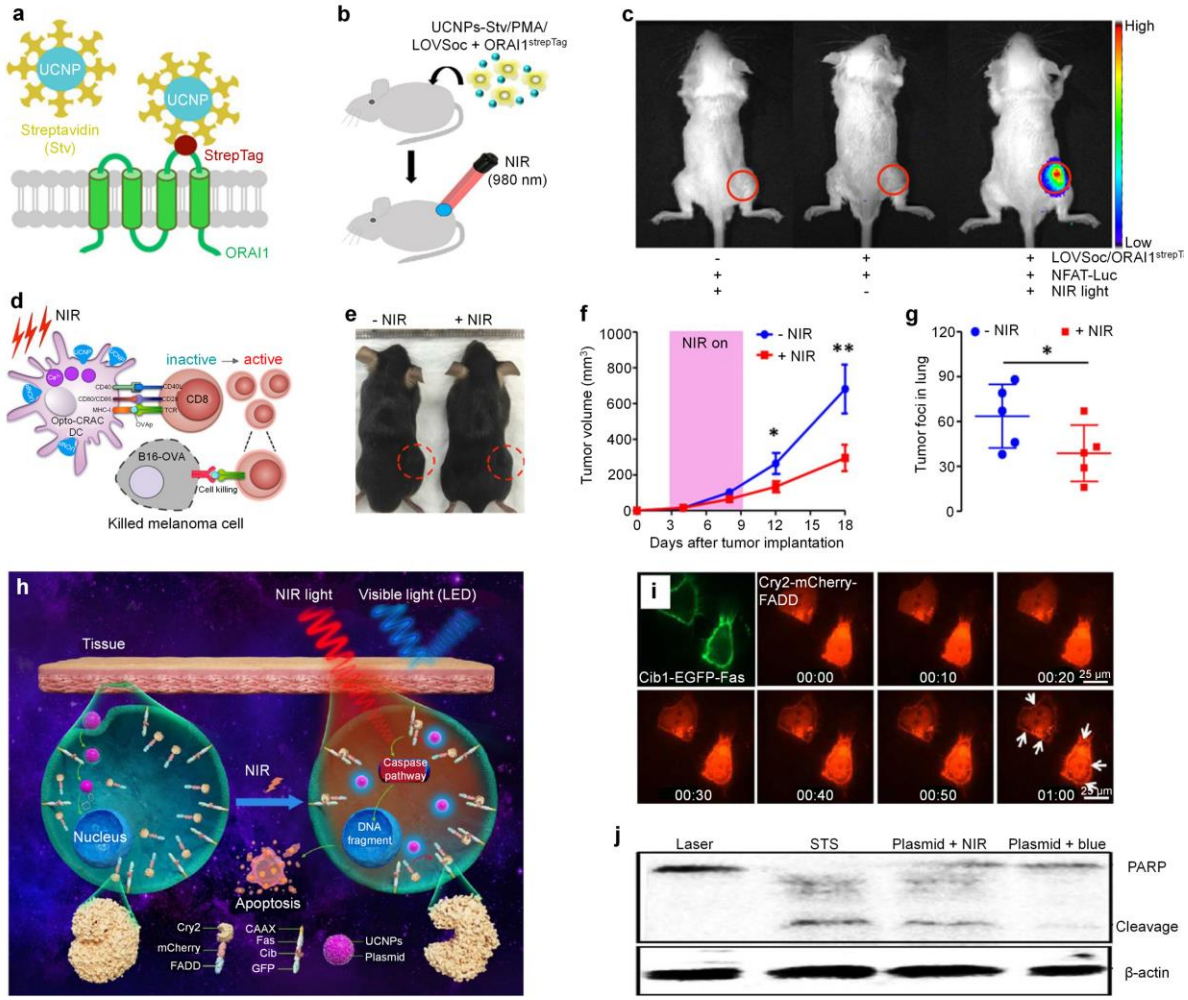


Figure 4. (a) Scheme of interaction between streptavidin-conjugated UCNPs and the engineered ORAI1 Ca^{2+} channel that harbored a streptavidin-binding tag (StrepTag) in the second extracellular loop. (b) Scheme of NFAT-dependent luciferase expression *in vivo* triggered by NIR light irradiation. (c) Bioluminescence imaging of three representative BALB/c mice, one implanted with HeLa cells expressing NFAT-Luc only (left) and the other two with cells expressing LOVSoc and NFAT-Luc (middle and right). Mice were subjected to NIR light irradiation (left and right) with a 980 nm laser. Red circle indicated implanted area. (d) Scheme of NIR-stimulated Ca^{2+} influx in Opto-CRAC DCs to prompt immature DC maturation and boost anti-tumor immune responses. (e) Tumor-inoculated sites shielded or exposed to NIR laser irradiation. (f) The tumor growth curves after different treatments. (g) The numbers of tumor metastases in lungs of mice after treatments. (h) Scheme for application of the UCNP-mediated optogenetic nanosystem. (i) After Fas-Cib1-EGFP and Cry2-mCherry-FADD constructs (1:2 ratio) were cotransfected in HeLa cells using UCNPs for 48 h, they were irradiated outside of 2 mm pork tissue using NIR light (980 nm, 4 W). The time course of Cry2-mCherry-FADD recruitment to Fas-Cib1-EGFP on the plasma membranes was observed under

confocal microscopy. (j) Western blots of light-triggered formation of cleaved poly(ADP-ribose) polymerase (PARP) fragment in HeLa cells at 48 h post-light exposure after treatment with a 4 W NIR laser or blue LED irradiation for 2 h (10 s every 1 min). (a)-(g) Reprinted with permission.[107] Copyright 2015, eLife Sciences Publications. (h)-(j) Reprinted with permission.[108] Copyright 2017, American Chemical Society.

3.2. Photothermic gene expression

Since living cells are known to be sensitive to temperature changes in different perspectives, nanomaterial-mediated local photothermal stimulation within the physiological ranges can be utilized to control cell behaviors through regulating intracellular gene transcription.[109, 110] For example, Lim and Cho et al. recently reported the photothermic activation of receptor-ligand multivalent interactions to enable dynamic regulation of stem cell differentiation.[110] This was demonstrated through treating human neural stem cells (hNSCs) with single-walled carbon nanotubes (SWCNTs) noncovalently assembled with RGD peptides and thermos-responsive dendrimers. Photothermal heating of these SWCNTs induced the shrinkage of the thermoresponsive dendrimers owing to their lower critical solution temperature (LCST) behavior, which triggered the surface presentation of RGD peptides to enable their bindings with β1-integrins on the membranes of hNSCs. As such, this RGD-integrin receptor clustering up-regulated the gene expression of neuronal biomarkers (Tuj1 and MAP2) and promoted the differentiation of hNSCs into electrophysiologically functional neurons.

The mild temperature increments can also facilitate up-regulation of some thermosensitive biomolecules in living biological systems, such as heat shock protein, which turns on gene transcription. As reported by Ciofani's group, photothermal conversion of gold nanoshells (AuNSHs) under NIR laser irradiation at 808 nm was exploited to remotely activate striated muscle cells through up-regulating related gene expression.[111] In their study, the chronic remote photothermal stimulation wirelessly up-regulated the mRNA transcription of genes

encoding heat shock proteins and sirtuin 1 (SIRT1), a protein which in turn induced mitochondrial biogenesis.

In addition to endogenous genes, nanomaterial-mediated local photothermal stimulation can upregulate the expression of various exogenous genes of interest inserted downstream of the heat shock promoters (HSP), providing a useful tool to treat inherited genetic diseases and cancers. In this regard, Pu' group reported the development of a NIR absorbing dendronized semiconducting polymer (DSP) and utilized it as a photothermal nanocarrier and intracellular nanotransducer for remote photoregulation of gene expression in living cells and animals.[112] Such a DSP comprised hydrophobic semiconducting polymer (SP2) backbone, cationic third-generation polyamidoamine (PAMAM3) side chains and neural PEG blocks, in which, these components served as the NIR photothermal nanotransducer, gene vector and water-solubility enhancer, respectively (**Figure 5**a). To achieve efficient delivery of genes, plasmids with the incorporation of genes of interest cloned downstream of a heat-inducible promoter (HSP70) were complexed with DSP, affording nanocomplexes. After cellular internalization, plasmids were released from the nanocomplexes and entered into cellular nucleus, while DSP retained in the cytoplasm. Upon laser irradiation at 808 nm, DSP generated local mild heat, stimulating the HSP70 promoter to activate transcription of downstream genes (Figure 5b). Using luciferase plasmid (pSV40-Luc) as the model gene, such DSP-mediated photothermal activation rapidly triggered 25- and 4.5-fold increments in the expression of luciferase in living cells and mice, respectively (Figure 5c-f). Another two similar studies also presented the use of CNHs and SPNs for photothermic activation of gene expression.[113, 114] Modification of nanomaterials with Tat peptide (RKKRRQRRRC) allowed their location on the surface of cell membranes, which could improve the specificity and efficiency for photoactivated gene expression. While, all these nanomaterials were simply utilized as the transducers for heating and gene delivery systems were required to be conducted in a separate step.

Using a tumor suppressor gene (*e.g.* p53) as the target gene, Chang and coworkers demonstrated that nanomaterial-mediated photothermic activation of gene transcription could be adopted for gene therapy of tumors.[115] In their work, the therapeutic plasmid DNA (pDNA) designed to contain HSP70 as the promoter, green fluorescent protein (GFP) as the reporter gene, and tumor suppressor p53 gene as the encoded target gene, were loaded into polyethyleneimine-modified Prussian blue nanocubes (PB@PEI NCs). Owing to the excellent photothermal conversion property of PB NCs, mild NIR laser irradiation at 808 nm increased the temperature to ~41 °C, which stimulated the HSP70 promoter to activate the expression of p53 protein and led to the apoptosis of cancer cells. Such a p53-dependent gene therapy synergized with PTT by adjusting the level of the photothermal effect at temperature from ~41 to ~50 °C, achieving significant cell damage and tumor growth inhibition.

Nanomaterial-mediated local photothermal effect has also been utilized as a stimulus for the control of Ca^{2+}-dependent gene expression. In this case, following NIR laser irradiation, the increase in local temperature opens the TRPV1 ion channels or triggers the cell membrane permeabilization to allow Ca^{2+} influx; the increased cytosolic Ca^{2+} activates Ca^{2+} responsive gene elements in Ca^{2+}-dependent signaling pathway, which induces downstream expression of genes of interest.[116] This photothermal genic switching strategy has recently been adopted by Tang's group, to locally and temporally impede the progression of atherosclerosis.[117] In their work, copper sulfide (CuS) NPs conjugated with anti-TRPV1 antibodies were used as remote transducers to specifically bind to TRPV1 on the plasma membrane of vascular smooth muscle cells (VSMCs), allowing a local temperature increase upon 980 nm NIR laser irradiation. This local heating triggered opening of TRPV1 ion channels and influx of Ca^{2+}, subsequently initiated the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK)-associated autophagy and upregulation of adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) gene expression, and eventually resulted in enhanced cholesterol efflux and decreased lipid accumulation and foam cell formation in the oxidized low-density

lipoprotein (oxLDL)-treated VSMCs (Figure 5g,h). More importantly, CuS-anti-TRPV1 was used to target aortic arch after the intravenous administration, affording a desirable therapeutic efficiency in obviously reducing lipid storage and atherosclerotic lesions in the aortic arch of plaque-bearing apolipoprotein E knockout (ApoE−/−) mice (Figure 5i).

Nanomaterial-mediated photothermal conversions can enable the controlled delivery of bioactive modulators from temperature-responsive carriers, which makes remote manipulation of gene expression and intracellular signaling pathways feasible. For instance, Tortiglione and Parak et al. constructed a temperature-responsive polyelectrolyte multilayer nanocapsule containing Au nanoparticles as the photothermal agents to mediate capsule wall opening upon NIR laser irradiation, allowing the local delivery of alkaline phosphatase (ALP) in Hydra to trigger the activation of Wnt/β-catenin molecular signaling pathway.[118] In another study, Chen and coworkers developed a temperature-responsive protein delivery system by conjugating a protein complex of growth factor β (TGF-β) with SWCNT through a homodimer of the latency-associated peptide (LAP), in which, TGF-β was inactive.[74] Upon NIR laser irradiation at 980 nm, TGF-β was released from LAP *via* the photothermal effect of SWCNTs and became active; the activated TGF-β bound with TGF-β receptors on the cell surfaces, consequently activating intracellular small mothers against decapentaplegic (SMAD) protein complexes to modulate relevant gene transcription. Such a photothermal-mediated TGF-β signal transduction activation was able to activate the epithelial-mesenchymal transition (EMT) of normal murine mammary gland cells and protein expression in living mice.

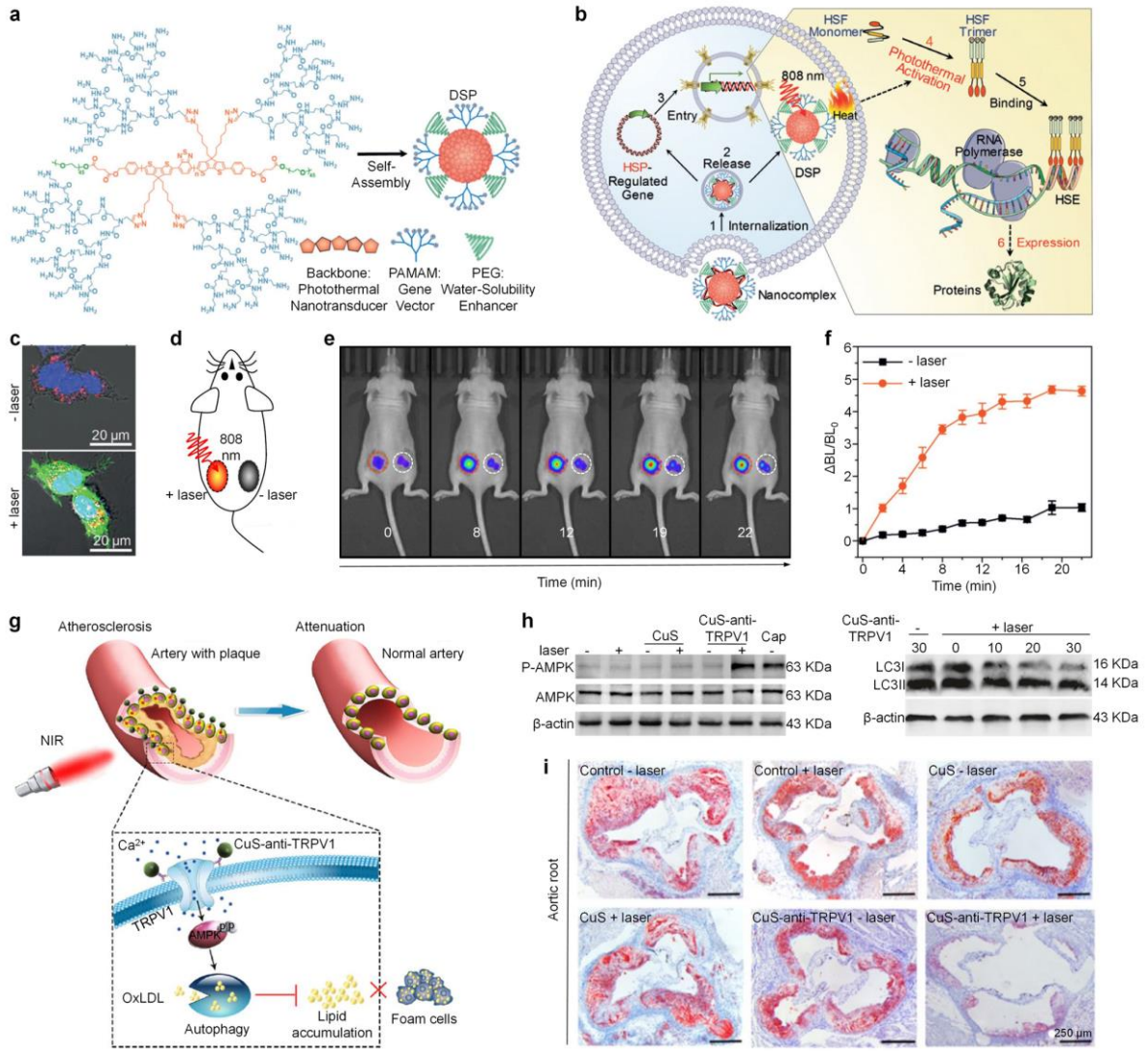


Figure 5. (a) Chemical structure and self-assembly of DSP. (b) Illustration of DSP-mediated gene delivery and remote photothermal activation of gene expression under 808 nm NIR laser irradiation. (c) Fluorescence images of HeLa cells after transfection with DSP/pHSP70-EGFP nanocomplexes with a N/P ratio of 7.5:1 with (+ laser) and without (- laser) laser irradiation at 808 nm for 30 min. (d) Illustration of laser irradiation in living nude mice. (e) Whole-animal bioluminescence (BL) images at representative times with (left side of animal) and without (right side of animal) laser irradiation at 808 nm. The red/white dashed circles indicated the respective regions subcutaneously implanted with the HeLa cells pellets transfected with DSP/pHSP70-Luc nanocomplexes and treated with/without 808 nm NIR laser irradiation. (f) Quantification of changes in the BL intensities as a function of time with (red) and without (black) NIR laser irradiation. (g) Illustration of CuS-anti-TRPV1 switch for the photothermal activation of TRPV1 signaling pathway to attenuate atherosclerosis. (h) Western blot analysis of AMPK phosphorylation and expression of LC3I and LC3II in VSMCs induced by CuS-anti-

TRPV1 heating-evoked Ca^{2+} influx. (i) Representative images of Oil Red O-stained aortic root sections. Haematoxylin was used as a counterstain. (a)-(f) Reprinted with permission.[112] Copyright 2017, John Wiley & Sons Ltd. (g)-(i) Reprinted with permission.[117] Copyright 2018, Nature Publishing Group.

3.3. Activation of photocaged transgenic systems

Controlling the activity of exogenous nucleic acids and other biomolecules in specific cells by light has been another promising means to regulate transgenic systems and cellular behaviors. Photoregulations of nucleic acids have been realized in a way involving its caging using a photolabile moiety and then uncaging and releasing at the desired sites and times upon irradiation of light at a specific wavelength.[119, 120] This method was recently reported by Zhang et al. to control gene expression and knockdown.[121] Plasmid DNA and siRNA were caged with UV light-sensitive 1-(4,5-dimethoxy-2-nitrophenyl)diazoethane (DMNPE) to block their activity and then loaded into mesoporous silica-coated $NaYF_4$:Yb,Er UCNPs. Upon NIR laser irradiation at 980 nm, UCNPs were able to emitted UV light locally to restore the activity of nucleic acids, resulting in the expression and knockdown of GFP in cells and animal models. Similarly, Bian et al. encapsulated DMNPE/siRNA into mesoporous silica-coated UCNPs and conjugated them with an enzyme cleavable imaging unit for remote regulation of stem cell differentiation as well as simultaneous monitoring of differentiation processes.[122]

In addition to photocaged nucleic acids, Zhang's group recently reported the utilization of photomorpholinos for NIR light-triggered regulation of both gene expression and gene knockdown.[123-125] Photomorpholinos are nonfunctional morpholinos incorporated with photocleavable moieties, which become active upon UV irradiation. For instance, mesoporous silica-coated $NaYF_4$:Yb,Tm@$NaYF_4$:Yb,Er UCNPs that emitted both the UV and visible light were synthesized and co-loaded with an anti-signal transducer and activator of transcription 3 (STAT-3) photomorpholino and an endosome localizing photosensitizer mesotetraphenylporphyrin (TPPS2a). The UCNP-emitted UV light activated the

photomorpholino to participate in RNA interference, while the visible light activated TPPS2a to disrupt endosomal membranes and enhance photomorpholino delivery. As a result, these UCNPs delivered into B16F0 cells and tumor models in living mice were reported to enhance the endosomal escape and knockdown the expression of STAT-3 upon NIR laser irradiation.

By taking advantage of light-responsive property of photocleavable caging, controlled releases of genic modulators in cells of interest have been demonstrated to allow remote regulations of gene expression and cellular functions.[126, 127] In an interesting work, Bian and coworkers developed a UCNP-based carrier with photocleavable uncaging capability for NIR light-mediated control of intracellular Ca^{2+} levels to regulate the macrophage polarization.[128] Mesoporous silica-coated UCNPs were loaded with either 1-(4,5-dimethoxy-2-nitrophenyl)-1,2-diaminoethane-N,N,N',N'-tetraacetic acid (caged Ca^{2+}, DMNP-EDTA-Ca^{2+} complex) that served as the Ca^{2+} supplier or 1,2-bis(2-aminophenoxy) ethane-N,N,N',N'-tetraacetic acid tetrakis(acetoxymethyl ester) (BAPTA-AM) that served as the Ca^{2+} chelator, which were further conjugated with RGD peptide-bearing molecular caps *via* a UV photolabile linker as the photosensitive gating structure. NIR laser irradiation at 980 nm enabled on-demand release of Ca^{2+} regulators *via* cleavage of the photosensitive caps and modulation of intracellular Ca^{2+} levels, which regulated relevant gene expression, thereby promoting M1 or M2 polarization of macrophages.

Bian's group also loaded a chondro-inductive kartogenin (KGN) into these photocleavable nanocarriers to demonstrate their applications in tissue engineering.[129] RGD-integrin bindings facilitated internalization of these UCNP-based nanocomplexes into bone marrow-derived human mesenchymal stem cells (hMSCs), wherein this NIR-to-UV light conversion triggered an intracellular photo-uncaging and release of cargo molecules to remotely control the intracellular Ca^{2+} levels and regulate stem cell differentiation (**Figure 6**a). Importantly, *in vivo* remote regulation of differentiation of hMSCs could be achieved by encapsulating these nanocomplexes within hyaluronic acid hydrogels for subcutaneous implantation. Such a NIR-

triggered delivery of KGN alone activated the differentiation of hMSCs into hypertrophic chondrocytes (Figure 6b), whereas NIR-triggered co-delivery of Ca^{2+} chelators and KGN induced the differentiation of hMSCs to classic chondrocytes by inhibiting their hypertrophy (Figure 6c). Conversely, NIR-triggered co-delivery of Ca^{2+} suppliers and KGN promoted the differentiation of hMSCs into osteoblasts (Figure 6d).

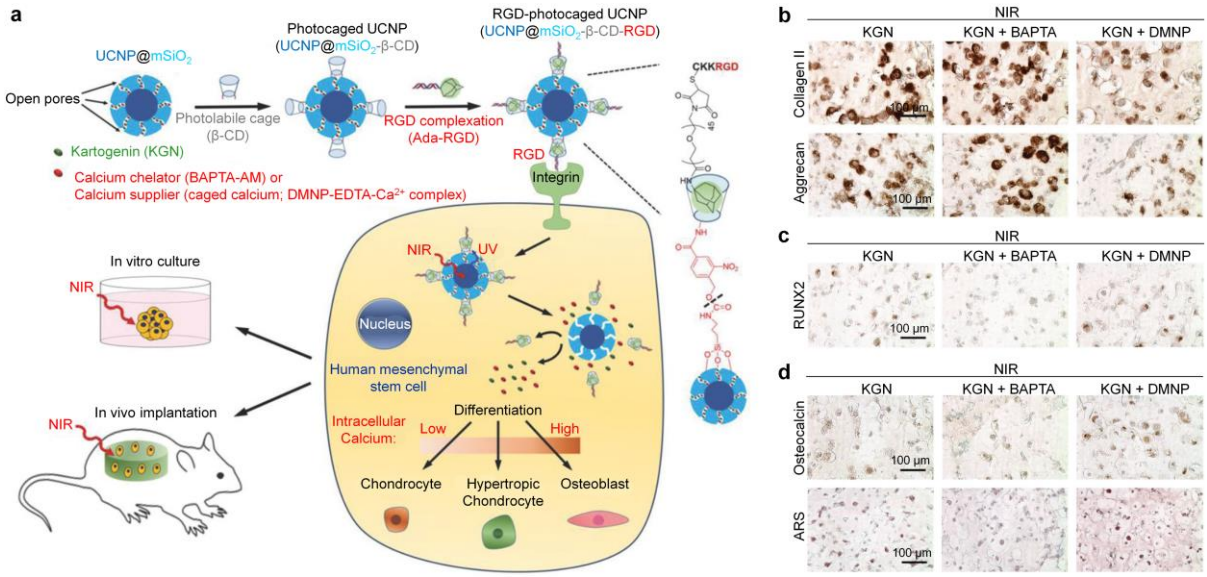


Figure 6. (a) NIR light-mediated control of photo-uncaging and intracellular release of KGN and/or either Ca^{2+} chelators or Ca^{2+} suppliers by UCNP-based nanocomplexes, both *in vitro* and *in vivo*. Integrin-binding RGD ligand was complexed with the photocaged UCNPs to allow their direct and effective regulation of intracellular Ca^{2+} by NIR light, to regulate stem cell differentiation. Immunohistochemical staining of (b) chondrocyte markers (collagen II and Aggrecan), (c) hypertrophic chondrocyte markers (RUNX2) and (d) osteoblast marker (Osteocalcin) and Alizarin Red S (ARS) staining at 21 d after implantation. The hMSCs were labeled with UCNP@$mSiO_2$-β-CD-RGD containing KGN alone ("KGN"), KGN and BAPTA ("KGN + BAPTA"), or KGN and DMNP ("KGN + DMNP") before implantation. NIR laser irradiation (980 nm) at 1.0 W/cm^2 was applied to the treated hMSCs in living mice for 5 min immediately after implantation. Reprinted with permission.[129] Copyright 2018, John Wiley & Sons Ltd.

4. Photoregulation of visual systems

Vision is an important sensory modality for mammals.[130] The degeneration of photoreceptors in the retina often leads to blindness.[131] It has shown that the use of optical materials can activate the reinstatement of vision. As an example, Benfenati and colleagues recently fabricated a completely organic prosthesis composed of a silk substrate covered with photoactive layers of semiconducting polymers and implanted it into the sub-retinal space of dystrophic Royal College of Surgeons (RCS) rats, a widely recognized model of retinitis pigmentosa.[131] This was reported to allow a significant recovery of light sensitivity and visual acuity that persisted up to 6-10 months after implantation.

In addition to visual reinstatement, optical nanotransducers can activate photoreceptors to allow mammals to even see NIR light (Table 1). This idea was recently validated by Xue and Han et al. *via* injecting photoreceptor-binding UCNPs (pbUCNPs) into the sub-retinal space in the eyes of mice.[132] To match the most sensitive visible light of eyes at an electromagnetic wavelength of ~550 nm, $NaYF_4$:Yb,Er@$NaYF_4$ core-shell-structured UCNPs with an emission peak at 535 nm upon 980 nm NIR light irradiation were conjugated with concanavalin A protein (ConA) to generate pbUCNPs (**Figure 7**a). Since ConA could bind to sugar residues and derivatives of the photoreceptor outer segment through forming glyosidic bonds, such pbUCNPs had the capability of anchoring and binding to the photoreceptors in the mouse retina (Figure 7b). The rods of pbUCNP-injected mice under 980 nm NIR light irradiation had similar photocurrents to those for the pbUCNP-injected and non-injected mice under normal visible light (535 nm) irradiation, while the rods from non-injected mice under 980 nm NIR light irradiation showed no responses (Figure 7c), suggesting NIR light mediated activation of photoreceptors. As such, pbUCNP-treated mice could consciously perceive NIR light as witnessed by the observation that they exhibited a significant preference for the dark box in the light-dark box experiments, while the non-treated control mice could not distinguish between the 980 nm NIR light-illuminated and dark boxes (Figure 7d). In the Y-shaped water maze behavioral experiments, it was further confirmed that pbUCNP-treated mice had acquired NIR

light image visual ability by recording their visually evoked potential (VEP) and obtained NIR light pattern vision. After training with 980 nm light gratings, the pbUCNP-injected mice could distinguish the two different orientations (vertical and horizontal) of NIR light gratings, whereas the non-injected control mice made such choices in a random manner (Figure 7e-h). The mice trained with visible light gratings in the parallel control groups were also able to find the associated platform regardless of the injection of pbUCNPs. Moreover, the implantation of pbUCNPs was reported to not cause retinal degeneration, inflammation, cell apoptosis or any other long-term side effects.

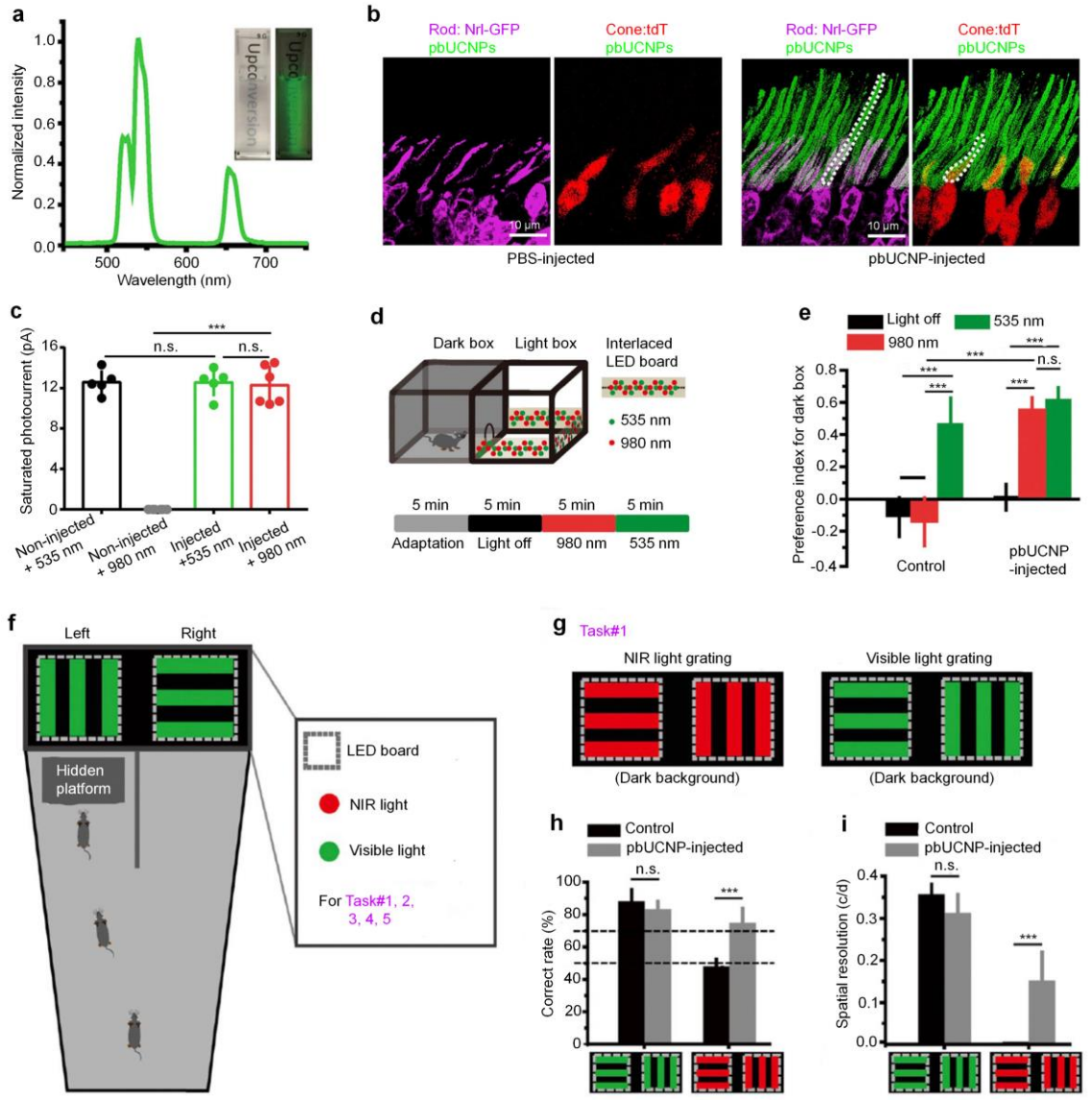


Figure 7. (a) Emission spectrum of UCNPs upon 980-nm continuous wave (CW) NIR laser irradiation. Inset displays photographs of UCNP solutions with (right) and without (left) 980-nm laser excitation. (b) Overlaid green (pbUCNPs)/violet (rods) and green (pbUCNPs)/red (cones) channel fluorescence images of retina from PBS-injected mice (left) and pbUCNP-injected mice (right). Examples of continuous inner and outer segments of a rod and a cone are shown in dashed contour lines. (c) Saturated photocurrent of rods from non-injected mice with 535-nm or 980-nm light stimulations and pbUCNP-injected mice with 535-nm or 980-nm light stimulations. (d) Light-dark box experiment diagram. Light box was illuminated with an array of LED light interlaced by 980-nm and 535-nm LEDs. Illumination protocol is shown at the bottom. Each section contained four episodes and each episode was 5 min long. The first 5-min episode was adaptation in the light-dark box with an ambient light followed by a 5-min episode in complete darkness. The 980-nm and 535-nm LEDs were then lit consecutively for the light box for 5 min each. (e) Preference index for dark box under three different light box conditions (light off, 980 nm, and 535 nm). Preference index = (time spent in dark box - in light box)/(time spent in dark box + in light box). (f) Diagram of Y-shaped water maze behavioral experiments for Tasks 1-5. (g) Stimuli of Task 1. Experiments were under dark background. (h) Correct rates of Task 1 for light grating discrimination. (i) Visual spatial resolutions of pbUCNP-injected and control mice for 535-nm and 980-nm light gratings. Reprinted with permission.[132] Copyright 2019, Elsevier Inc.

5. Photochemical tissue bonding

Photochemical tissue bonding (PTB), a novel noninvasive technique that combines light with photosensitizers for wound tissue repair, has been regarded as a potential alternative to traditional stapling and suturing.[133] PTB relies on the photoactivation of photosensitizers to release reactive species, creating effective cross-linking between apposed tissue surfaces. Current PTB is often performed employing Rose Bengal (RB) as the photosensitizer in

damaged tissue and subsequently irradiating in situ with green light, which has been used to repair a variety of tissues including skin, blood vessels, vocal cords, cornea, and peripheral nerves.[134] Nevertheless, the shallow tissue penetration depth of green light is a serious limitation, making it challenging for clinical applications.

To overcome the penetrating limitation of exciting light, Hahn and Kim et al. developed a conjugate nanocomplex containing poly(allylamine) (PAAm)-modified UCNPs, hyaluronate (HA) and RB (termed as UCNP/PAAm/HA-RB) and used it for deep-tissue PTB under NIR light illumination (**Figure 8**a).[135] In such nanocomplexes, the outer HA layer allowed them to be transdermally delivered into a deep and wide area from the boundary of incision, because HA could hydrate the skin barrier and penetrate through the skin, as well as target the highly expressed HA receptors in skin tissues. Upon 980 nm light irradiation, UCNP cores converted the NIR light into green light to activate RB, resulting in an accelerated collagen cross-linking in the porcine skin (Figure 8b,c). Additionally, such a UCNP-mediated PTB technique with NIR light irradiation afforded 2.1- and 1.6-fold faster tissue bonding of incision on the dorsal skin of mice as compared to the HA-RB conjugate group with green light irradiation and conventional suturing, respectively (Figure 8d,e).

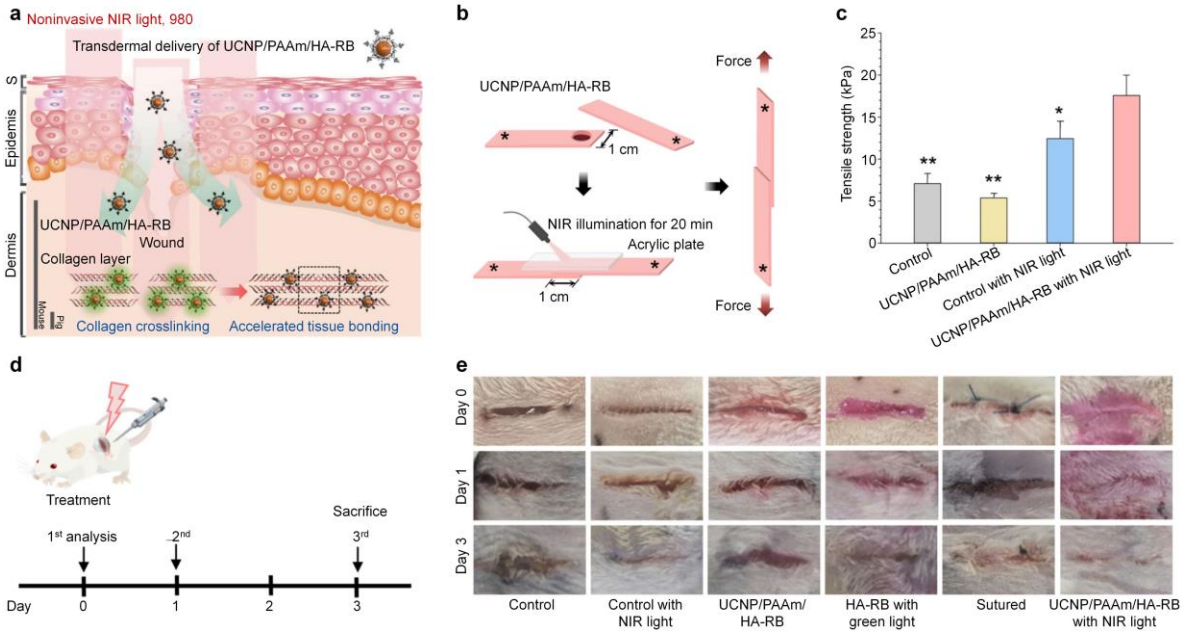


Figure 8. (a) Schematic illustration for photochemical tissue bonding of the incised collagen matrix by NIR light irradiation after transdermal delivery of UCNP/PAAm/HA-RB conjugate nanocomplexes. (b) Schematic illustration for the *ex vivo* tensile strength test to assess the photochemical tissue bonding of porcine skin. (c) Tensile strength of adhered tissues by the treatment of the control (PBS), UCNP/PAAm/HA-RB conjugate nanocomplex, PBS with NIR light irradiation and UCNP/PAAm/HA-RB conjugate nanocomplex with NIR light irradiation. (d) Schematic illustration for *in vivo* PTB test with three analyses before sacrifice for tensile strength test. (e) Photographs of the incised dorsal skin of BALB/c mice after treatments of PBS (control), PBS with NIR light irradiation, UCNP/PAAm/HA-RB conjugate nanocomplex, HA-RB conjugate with green light irradiation, suturing, and UCNP/PAAm/HA-RB conjugate nanocomplex with NIR light irradiation at day 0, 1, and 3. Reprinted with permission.[135] Copyright 2017, American Chemical Society.

Table 1. Summary of optical nanotransducers for NIR photoregulation in biomedicine.

Nanomaterials	Light source	Property	Applications	Refs
$NaYF_4$:Sc/Yb/Er UCNPs	975 nm	NIR-to-green light upconversion	Optogenetic activation of ND7/23 neural cells	[85]
$NaYF_4$:Yb/Tm@ $NaYF_4$ UCNPs	980 nm	NIR-to-blue light upconversion	Optogenetic activation of ChR2-expressing neurons, photoregulation of Ca^{2+}-dependent gene expression and DC-mediated immunotherapy	[86, 89, 107]
$NaYF_4$:Yb/Er@ $NaYF_4$:Yb@IR-806	800 nm	NIR-to-red light upconversion	Robust activation of hippocampal neurons expressing ReaChR	[87]
$NaYF_4$:Yb/Tm@ SiO_2 UCNPs	980 nm	NIR-to-blue light upconversion	*In vivo* optogenetic activation of ChR2-transfected neurons	[88]
$NaYF_4$:Yb/Er@ SiO_2 UCNPs	980 nm	NIR-to-green light upconversion	*In vivo* inhibition of hippocampal neurons expressing Arch	[88]
$NaYF_4$:Yb/Er@ $NaYF_4$	980 nm	NIR-to-green light upconversion	*In vivo* optogenetic activation of rat brain neurons expressing ChR2 or C1V1	[89]
$NaYF_4$@$NaYF_4$:Yb /Er@$NaYF_4$	980 nm	NIR-to-green light upconversion	Inhibition of NpHR-expressing neurons, suppression of secondary motor cortex in behaving mice and locomotion behavior	[91]
CNHs@IR800	800 nm	Photothermal effect	Photothermal activation of Ca^{2+} flux and membrane currents of neurons	[93]

AuNRs	780 or 980 nm	Photothermal effect	Photothermal activation of TRPV1 ion channel, stimulation of primary auditory neurons, remote activation of neural tissues, photothermal inhibition of temperature-sensitive TREK-1 channel and neuron activity	[94-96, 99, 100]
Liquid metal nanocapsules	808 nm	Photothermal effect	Photothermal regulation of TRPV1 ion channel activity	[97]
$SPN1_{bc}$	808 nm	TRPV1 targeting, photothermal effect,	Targeted photothermal activation of TRPV1 ion channel in neurons	[98]
AuNSs	808 nm	Photothermal effect	Photothermal suppression of neuronal spiking activity	[101]
$NaYF_4$:Yb,Tm@ $NaGdF_4$:Yb UCNPs	980 nm	NIR-to-blue light upconversion	Optogenetic activation of apoptosis signaling pathway and inhibition of tumor growth	[108]
SWCNTs	808 nm	Photothermal effect	Photothermic activation of receptor-ligand multivalent interactions, gene expression and stem cell differentiation	[110]
AuSHs	808 nm	Photothermal effect	Photothermal activation of heat shock protein and sirtuin 1 gene expression and myotube activity	[111]
DSP	808 nm	Photothermal effect	Remote photothermal activation of targeting gene expression in living cells and animals	[112]
BSA-CNHs	785 nm	Photothermal effect	Photothermal activation of HSP-mediated gene expression systems	[113]
SPN-Tat	808 nm	Targeting ability, photothermal effect	Targeting photothermal activation of gene expression in living cells	[114]
PB@PEI NCs	808 nm	Photothermal effect	Photothermal activation of p53 gene expression for combinational cancer therapy	[115]
CuS-anti-TRPV1	980 nm	Photothermal effect	Photothermal activation of Ca^{2+}-dependent gene expression for attenuating atherosclerosis	[117]
Polyelectrolyte nanocapsules	830 nm	Photothermal effect	Photothermal release of ALP and activation of Wnt/β-catenin signaling related gene expression	[118]
SWCNT-LAP	980 nm	Photothermal effect	Photothermal release and activation of TGF-β and regulation of TGF-β signal transduction	[74]
$NaYF_4$:Yb,Er@ SiO_2 UCNPs	980 nm	NIR-to-UV light upconversion	Photo-uncaging of biomolecules and activation of gene expression and knockdown	[121]
UCNP-peptide-AIE	980 nm	NIR-to-UV light upconversion	Photoregulation of caged siRNA and induction of stem cell differentiation	[122]

$NaYF_4$:Yb,Tm@ $NaYF_4$:Yb,Er UCNPs	980 nm	NIR-to-UV/Vis light upconversion	Photoactivation of photomorpholino and knockdown gene expression of STAT-3	[123]
$NaYF_4$:Yb@SiO_2 UCNPs	980 nm	NIR-to-UV light upconversion	Photoregulation of intracellular Ca^{2+} and modulating of macrophage polarization	[128]
$NaYF_4$:Yb,Tm@ SiO_2 UCNPs	980 nm	NIR-to-UV light upconversion	Photoregulation of intracellular Ca^{2+} and photo-uncaging of biomolecules for stem cell differentiation regulation	[129]
$NaYF_4$:Yb,Er@ $NaYF_4$ UCNPs-ConA	980 nm	NIR-to-green light upconversion, retina targeting	Photoregulation of NIR light sensation, imaging visual pathway and pattern vision	[132]
UCNP/PAAm/HA-RB	980 nm	NIR-to-green light upconversion, ROS generating	Photoregulation of collagen crosslinking and noninvasive photochemical tissue bonding	[135]

6. Conclusions and Outlook

Biological photoregulation represents a promising remote-control approach to potentially enable many biomedical applications, ranging from cellular function regulation to cancer therapy and even tissue engineering. Compared with traditional technologies relying on UV/Vis light, NIR photoregulation has lower toxicity and deeper tissue penetration, and thereby is more suitable for in vivo applications. Since few endogenous biomolecules have been found to absorb or emit NIR light, exogenous transducers are generally required for effective NIR photoregulation. NIR nanomaterials can be modified to have desired interactions with different biological systems including nucleic acids, proteins, membranes, organelles and whole cells meanwhile to allow the well-controlled photo-energy transduction,[136] making them competent as key nanotransducers in the processes of photoregulation.

This progress report summarizes the recent development of nanotransducers for NIR light-mediated photoregulation. For instance, UCNPs can convert NIR light to UV/visible light to stimulate light-sensitive proteins, photocaged moieties, and retinal photoreceptors, allowing for remote activation of neuronal activity, gene transcription, signaling pathway, stem cell differentiation, immune response and ocular visual systems. Photosensitizer-based nanoparticles are capable of generating free radicals upon NIR light irradiation, which activates

collagen crosslinking and tissue bonding. Other optical nanomaterials, such as SPNs, liquid metal nanocapsules, SWCNTs, AuNRs and AuNSs exert photothermal heating capabilities, resulting in the regulation of ion channels, gene expression, signal transductions and cell behaviors.

Application of optical nanomaterials as nanotransducers for NIR photoregulation of biological events is only at the proof-of-concept stage, and several critical concerns are required to be addressed. First, because nanomaterials are known to accumulate in tissues after systemic administration and excrete slowly out of the body, their long-term safety and toxicity profiles still remain questionable.[137-141] Some efforts have been made to mitigate this critical issue.[142-144] For example, the particle size of nanomaterials can be reduced to the level below the renal filtration threshold (~5 nm), which guarantees the rapid clearance *via* urine excretion.[145, 146] Even though these ultrasmall nanomaterials are non-biodegradable, they can undergo fast metabolism to attenuate their accumulation into tissues and reduce the toxicity risk. Alternatively, rational designs of nanomaterials to endow their biodegradability are highly desired.[147-150] Shi's group has reported the biodegradation of inorganic silica nanomaterials through hybridizing them with biodegradable organic disulfide bonds or doping them with metal manganese ions.[151-153] We and others have also shown that molecular integrations of vinylene bond,[154] thiophene moiety,[155] imine bond,[156] or imidazole unit[157] into organic nanoparticles (SPNs) are able to facilitate their in vivo biodegradation and thus clearance.

Second, the tissue penetration depth of NIR light is still limited, although it has shown to be improved as compared to that of UV and visible lights. Thus, NIR photoregulation is more suitable for cultured cells and superficial tissues in living subjects.[158] Currently, several emerging options have provided leverage to offset this constraint. For example, modification of light delivery methods should be a solution, and this was presented by Kobayashi et al., who combined external and interstitial NIR light exposure to improve the light delivery into deep-

seated tissues.[159] In addition, nanomaterials with optical absorption in the second NIR window (1000-1800 nm) have been developed with further improved tissue penetration depth.[160-163]

Third, the photon conversion efficiencies of nanomaterials still need to be improved to promote effective photoregulation in biomedicine. A recent study discovered that attachments of NIR dyes onto the surface of lanthanide-doped UCNPs afforded a ~33,000-fold increase in their NIR-to-visible upconversion efficiency over bare UCNPs.[164] Some other methods, such as molecule acceptor doping,[165] light-harvesting unit integration,[166] and polydopamine coating[167] have shown great potential in increasing the photothermal conversion efficiencies of nanomaterials. In addition, the ROS production used for photochemical tissue bonding could be amplified through incorporation of photosensitizers into optical nanomaterials or molecular engineering of photosensitizers.[168-171]

In addition to neural activity, gene transcription, ocular visual systems, and tissue binding as exemplified above, nanomaterials-mediated photoregulation are expected to exert specific roles in other fields of biomedicine. In view of the existence of thermosensitive and photosensitive enzymes in living systems, photoregulation of enzymatic activities could provide a powerful mean to control intracellular biochemical reactions and signal transduction.[67, 72, 172-174] The emergence of photodegradable and photoswitched compounds can lead to photoactivation of prodrugs, which could facilitate precise medicine with high efficacies and minimum side effects.[175-178] Moreover, the photodynamic feature of optical nanomaterials provides the probabilities for photoactivation of photo-immunotherapy (PIT), which can selectively induce tumor destruction and reduce tumor recurrence with minimized damage to normal tissues.[179-181]

Acknowledgements

K.P. thanks Nanyang Technological University (Start-Up grant: M4081627) and Singapore Ministry of Education (Academic Research Fund Tier 1: RG133/15 M4011559 and Academic Research Fund Tier 2 MOE2016-T2-1-098) for the financial support.

Received: ((will be filled in by the editorial staff))
Revised: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

References

[1] N. Sonenberg, A. G. Hinnebusch, *Cell* **2009**, *136*, 731.
[2] X. Ai, L. Lyu, Y. Zhang, Y. Tang, J. Mu, F. Liu, Y. Zhou, Z. Zuo, G. Liu, B. Xing, *Angew. Chem. Int. Ed.* **2017**, *56*, 3031.
[3] S. A. Stanley, J. Sauer, R. S. Kane, J. S. Dordick, J. M. Friedman, *Nat. Med.* **2015**, *21*, 92.
[4] E. Miyako, S. A. Chechetka, M. Doi, E. Yuba, K. Kono, *Angew. Chem. Int. Ed.* **2015**, *54*, 9903.
[5] C. Monzel, C. Vicario, J. Piehler, M. Coppey, M. Dahan, *Chem. Sci.* **2017**, *8*, 7330.
[6] M. Rotherham, J. R. Henstock, O. Qutachi, A. J. El Haj, *Nanomedicine* **2018**, *14*, 173.
[7] M. A. Wheeler, C. J. Smith, M. Ottolini, B. S. Barker, A. M. Purohit, R. M. Grippo, R. P. Gaykema, A. J. Spano, M. P. Beenhakker, S. Kucenas, *Nat. Neurosci.* **2016**, *19*, 756.
[8] H. Kang, D. S. H. Wong, X. Yan, H. J. Jung, S. Kim, S. Lin, K. Wei, G. Li, V. P. Dravid, L. Bian, *ACS Nano* **2017**, *11*, 9636.
[9] A. Marino, M. Battaglini, D. De Pasquale, A. Degl'Innocenti, G. Ciofani, *Sci. Rep.* **2018**, *8*, 6257.
[10] J. H. Cui, K. Park, S. R. Park, B.-H. Min, *Tissue Eng.* **2006**, *12*, 75.
[11] J. H. Cui, S. R. Park, K. Park, B. H. Choi, B.-h. Min, *Tissue Eng.* **2007**, *13*, 351.
[12] J. Gričar, M. Zupančič, K. Čufar, G. Koch, U. Schmitt, P. Oven, *Ann. Bot.* **2006**, *97*, 943.
[13] A. Opitz, A. Falchier, C.-G. Yan, E. M. Yeagle, G. S. Linn, P. Megevand, A. Thielscher, M. P. Milham, A. D. Mehta, C. E. Schroeder, *Sci. Rep.* **2016**, *6*, 31236.
[14] N. Grossman, D. Bono, N. Dedic, S. B. Kodandaramaiah, A. Rudenko, H.-J. Suk, A. M. Cassara, E. Neufeld, N. Kuster, L.-H. Tsai, *Cell* **2017**, *169*, 1029.
[15] Y. Wang, L. Guo, *Front. Neurosci.* **2016**, *10*, 69.
[16] L. He, G. Si, J. Huang, A. D. Samuel, N. Perrimon, *Nature* **2018**, *555*, 103.
[17] K. H. Vining, D. J. Mooney, *Nat. Rev. Mol. Cell Biol.* **2017**, *18*, 728.
[18] J. L. Ruan, N. L. Tulloch, M. Saiget, S. L. Paige, M. V. Razumova, M. Regnier, K. C. Tung, G. Keller, L. Pabon, H. Reinecke, *Stem Cells* **2015**, *33*, 2148.
[19] P. T. Yin, S. Shah, N. J. Pasquale, O. B. Garbuzenko, T. Minko, K.-B. Lee, *Biomaterials* **2016**, *81*, 46.
[20] L. Chang, M. Howdyshell, W. C. Liao, C. L. Chiang, D. Gallego-Perez, Z. Yang, W. Lu, J. C. Byrd, N. Muthusamy, L. J. Lee, *Small* **2015**, *11*, 1818.
[21] M. Yamaguchi, A. Ito, A. Ono, Y. Kawabe, M. Kamihira, *ACS Synth. Biol.* **2013**, *3*, 273.
[22] P. K. Manikonda, P. Rajendra, D. Devendranath, B. Gunasekaran, R. Aradhya, R. Sashidhar, C. Subramanyam, *Neurosci. Lett.* **2007**, *413*, 145.
[23] M. H. Cho, E. J. Lee, M. Son, J.-H. Lee, D. Yoo, J.-w. Kim, S. W. Park, J.-S. Shin, J. Cheon, *Nat. Mater.* **2012**, *11*, 1038.

[24] J. H. Lee, E. S. Kim, M. H. Cho, M. Son, S. I. Yeon, J. S. Shin, J. Cheon, *Angew. Chem. Int. Ed.* **2010**, *49*, 5698.
[25] J. Dobson, *Nat. Nanotechnol.* **2008**, 3, 139.
[26] A. Tay, D. Di Carlo, *Nano Lett.* **2017**, *17*, 886.
[27] A. H. Lewis, J. Grandl, *Elife* **2015**, *4*, e12088.
[28] Ç. Atak, Ö. Çelik, A. Olgun, S. Alikamanoğlu, A. Rzakoulieva, *Biotechnol. Biotechnol. Equip.* **2007**, *21*, 166.
[29] Y. Zhu, Q. Yang, M. Yang, X. Zhan, F. Lan, J. He, Z. Gu, Y. Wu, *ACS Nano* **2017**, *11*, 3690.
[30] S. K. Boda, G. Thrivikraman, B. Basu, *J. Mater. Chem. B* **2015**, *3*, 3150.
[31] P. Jiang, Y. Zhang, C. Zhu, W. Zhang, Z. Mao, C. Gao, *Acta Biomater.* **2016**, *46*, 141.
[32] H. Xu, Z. P. Aguilar, L. Yang, M. Kuang, H. Duan, Y. Xiong, H. Wei, A. Wang, *Biomaterials* **2011**, *32*, 9758.
[33] H.-M. Yun, S.-J. Ahn, K.-R. Park, M.-J. Kim, J.-J. Kim, G.-Z. Jin, H.-W. Kim, E.-C. Kim, *Biomaterials* **2016**, *85*, 88.
[34] M. Antman-Passig, O. Shefi, *Nano Lett.* **2016**, *16*, 2567.
[35] Y. Gao, J. Lim, S.-H. Teoh, C. Xu, *Chem. Soc. Rev.* **2015**, *44*, 6306.
[36] H. Huang, S. Delikanli, H. Zeng, D. M. Ferkey, A. Pralle, *Nat. Nanotechnol.* **2010**, *5*, 602.
[37] J. Yao, J. Feng, J. Chen, *Asian J. Pharm. Sci.* **2016**, *11*, 585.
[38] E. Y. Salinas, J. C. Hu, K. Athanasiou, *Tissue Eng., Part B* **2018**, *24*, 345.
[39] S. R. MacEwan, A. Chilkoti, *Nano Lett.* **2012**, *12*, 3322.
[40] J. D. Wells, C. Kao, E. D. Jansen, P. E. Konrad, A. Mahadevan-Jansen, *J. Biomed. Opt.* **2005**, *10*, 064003.
[41] N. M. Idris, M. K. G. Jayakumar, A. Bansal, Y. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 1449.
[42] J. Li, X. Zhen, Y. Lyu, Y. Jiang, J. Huang, K. Pu, *ACS Nano* **2018**, *12*, 8520.
[43] Y. Jiang, K. Pu, *Acc. Chem. Res.* **2018**, *51*, 1840.
[44] J. Li, K. Pu, *Chem. Soc. Rev.* **2019**, *48*, 38.
[45] Y. Wang, L. Feng, S. Wang, *Adv. Funct. Mater.* **2018**, *29*, 1806818.
[46] J. Li, J. Rao, K. Pu, *Biomaterials* **2018**, *155*, 217.
[47] H. Yang, J. Zhao, C. Wu, C. Ye, D. Zou, S. Wang, *Chem. Eng. J.* **2018**, *351*, 548.
[48] C. Wu, J. Zhao, F. Hu, Y. Zheng, H. Yang, S. Pan, S. Shi, X. Chen, S. Wang, *Carbohydr. Polym.* **2018**, *180*, 112.
[49] J. Wei, J. Li, D. Sun, Q. Li, J. Ma, X. Chen, X. Zhu, N. Zheng, *Adv. Funct. Mater.* **2018**, *28*, 1706310.
[50] C. Qian, J. Yu, Y. Chen, Q. Hu, X. Xiao, W. Sun, C. Wang, P. Feng, Q. D. Shen, Z. Gu, *Adv. Mater.* **2016**, *28*, 3313.
[51] H. Zhu, J. Li, X. Qi, P. Chen, K. Pu, *Nano Lett.* **2017**, *18*, 586.
[52] R. Chai, C. Xing, D. Gao, H. Yuan, Y. Zhan, S. Wang, *Adv. Healthcare Mater.* **2018**, *7*, 1800674.
[53] H. Dana, B. Mohar, Y. Sun, S. Narayan, A. Gordus, J. P. Hasseman, G. Tsegaye, G. T. Holt, A. Hu, D. Walpita, *Elife* **2016**, *5*, e12727.
[54] E. Reichhart, A. Ingles-Prieto, A. M. Tichy, C. McKenzie, H. Janovjak, *Angew. Chem. Int. Ed.* **2016**, *55*, 6339.
[55] J. Zhao, S. Lin, Y. Huang, J. Zhao, P. R. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 7410.
[56] Y.-Y. He, J.-L. Huang, C. F. Chignell, *J. Biol. Chem.* **2004**, *279*, 53867.
[57] P. C. Ford, *Coord. Chem. Rev.* **2018**, *376*, 548.
[58] Z. Chen, R. Thiramanas, M. Schwendy, C. Xie, S. H. Parekh, V. Mailänder, S. Wu, *Small* **2017**, *13*, 1700997.
[59] J. Jang, T. G. Kim, B. S. Kim, S.-W. Kim, S.-M. Kwon, D.-W. Cho, *Acta Biomater.* **2016**, *33*, 88.

[60] G. Yang, X. Sun, J. Liu, L. Feng, Z. Liu, *Adv. Funct. Mater.* **2016**, *26*, 4722.
[61] X. Zhen, C. Xie, Y. Jiang, X. Ai, B. Xing, K. Pu, *Nano Lett.* **2018**, *18*, 1498.
[62] S. Mura, J. Nicolas, P. Couvreur, *Nat. Mater.* **2013**, *12*, 991.
[63] M. K. Gnanasammandhan, N. M. Idris, A. Bansal, K. Huang, Y. Zhang, *Nat. Protoc.* **2016**, *11*, 688.
[64] J. S. Katz, J. A. Burdick, *Macromol. Biosci.* **2010**, *10*, 339.
[65] A. L. Antaris, H. Chen, K. Cheng, Y. Sun, G. Hong, C. Qu, S. Diao, Z. Deng, X. Hu, B. Zhang, X. Zhang, O. K. Yaghi, Z. R. Alamparambil, X. Hong, Z. Cheng, H. Dai, *Nat. Mater.* **2016**, *15*, 235.
[66] M. Karimi, P. Sahandi Zangabad, S. Baghaee-Ravari, M. Ghazadeh, H. Mirshekari, M. R. Hamblin, *J. Am. Chem. Soc.* **2017**, *139*, 4584.
[67] J. Li, J. Huang, Y. Lyu, J. Huang, Y. Jiang, C. Xie, K. Pu, *J. Am. Chem. Soc.* **2019**, *141*, 4073.
[68] Q. Miao, K. Pu, *Adv. Mater.* **2018**, *30*, 1801778.
[69] S. Wu, H. J. Butt, *Adv. Mater.* **2016**, *28*, 1208.
[70] Z. Chen, S. He, H. J. Butt, S. Wu, *Adv. Mater.* **2015**, *27*, 2203.
[71] T. Senthilkumar, L. Zhou, Q. Gu, L. Liu, F. Lv, S. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 13114.
[72] J. Li, C. Xie, J. Huang, Y. Jiang, Q. Miao, K. Pu, *Angew. Chem. Int. Ed.* **2018**, *57*, 3995.
[73] M. Li, X. Yang, J. Ren, K. Qu, X. Qu, *Adv. Mater.* **2012**, *24*, 1722.
[74] L. Lin, L. Liu, B. Zhao, R. Xie, W. Lin, H. Li, Y. Li, M. Shi, Y.-G. Chen, T. A. Springer, X. Chen, *Nat. Nanotechnol.* **2015**, *10*, 465.
[75] M. D. Blankschien, L. A. Pretzer, R. Huschka, N. J. Halas, R. Gonzalez, M. S. Wong, *ACS Nano* **2012**, *7*, 654.
[76] B. Q. Spring, R. B. Sears, L. Z. Zheng, Z. Mai, R. Watanabe, M. E. Sherwood, D. A. Schoenfeld, B. W. Pogue, S. P. Pereira, E. Villa, *Nat. Nanotechnol.* **2016**, *11*, 378.
[77] H. He, Y. Chen, Y. Li, Z. Song, Y. Zhong, R. Zhu, J. Cheng, L. Yin, *Adv. Funct. Mater.* **2018**, *28*, 1706710.
[78] J. Lee, D. G. Udugamasooriya, H.-S. Lim, T. Kodadek, *Nat. Chem. Biol.* **2010**, *6*, 258.
[79] A. T. Young, N. Cornwell, M. A. Daniele, *Adv. Funct. Mater.* **2018**, *28*, 1700239.
[80] E. S. Boyden, F. Zhang, E. Bamberg, G. Nagel, K. Deisseroth, *Nat. Neurosci.* **2005**, *8*, 1263.
[81] K. Huang, Q. Dou, X. J. Loh, *RSC Adv.* **2016**, *6*, 60896.
[82] J. Y. Lin, P. M. Knutsen, A. Muller, D. Kleinfeld, R. Y. Tsien, *Nat. Neurosci.* **2013**, *16*, 1499.
[83] H. Kim, Y. Park, S. Beack, S. Han, D. Jung, H. J. Cha, W. Kwon, S. K. Hahn, *Adv. Sci.* **2017**, *4*, 1700325.
[84] N. Yu, L. Huang, Y. Zhou, T. Xue, Z. Chen, G. Han, *Adv. Healthcare Mater.* **2019**, *8*, 1801132.
[85] S. Hososhima, H. Yuasa, T. Ishizuka, M. R. Hoque, T. Yamashita, A. Yamanaka, E. Sugano, H. Tomita, H. Yawo, *Sci. Rep.* **2015**, *5*, 16533.
[86] S. Shah, J.-J. Liu, N. Pasquale, J. Lai, H. McGowan, Z. P. Pang, K.-B. Lee, *Nanoscale* **2015**, *7*, 16571.
[87] X. Wu, Y. Zhang, K. Takle, O. Bilsel, Z. Li, H. Lee, Z. Zhang, D. Li, W. Fan, C. Duan, E. Chan, M., C. Lois, Y. Xiang, G. Han, *ACS Nano* **2016**, *10*, 1060.
[88] S. Chen, A. Z. Weitemier, X. Zeng, L. He, X. Wang, Y. Tao, A. J. Huang, Y. Hashimotodani, M. Kano, H. Iwasaki, L. K. Parajuli, S. Okabe, D. B. L. Teh, A. All, H., I. T. LKimura, K. F. Tanaka, X. Liu, T. J. McHugh, *Science* **2018**, *359*, 679.
[89] X. Lin, Y. Wang, X. Chen, R. Yang, Z. Wang, J. Feng, H. Wang, K. W. Lai, J. He, F. Wang, P. Shi, *Adv. Healthcare Mater.* **2017**, *6*, 1700446.
[90] J. V. Raimondo, L. Kay, T. J. Ellender, C. J. Akerman, *Nat. Neurosci.* **2012**, *15*, 1102.

[91] X. Lin, X. Chen, W. Zhang, T. Sun, P. Fang, Q. Liao, X. Chen, J. He, M. Liu, F. Wang, P. Shi, *Nano Lett.* **2018**, *18*, 948.
[92] J. L. Carvalho-de-Souza, J. S. Treger, B. Dang, S. B. Kent, D. R. Pepperberg, F. Bezanilla, *Neuron* **2015**, *86*, 207.
[93] E. Miyako, J. Russier, M. Mauro, C. Cebrian, H. Yawo, C. Ménard−Moyon, J. A. Hutchison, M. Yudasaka, S. Iijima, L. De Cola, A. Bianco, *Angew. Chem. Int. Ed.* **2014**, *53*, 13121.
[94] H. Nakatsuji, T. Numata, N. Morone, S. Kaneko, Y. Mori, H. Imahori, T. Murakami, *Angew. Chem. Int. Ed.* **2015**, *127*, 11725.
[95] J. Yong, K. Needham, W. G. Brown, B. A. Nayagam, S. L. McArthur, A. Yu, P. R. Stoddart, *Adv. Healthcare Mater.* **2014**, *3*, 1862.
[96] K. Eom, J. Kim, J. M. Choi, T. Kang, J. W. Chang, K. M. Byun, S. B. Jun, S. J. Kim, *Small* **2014**, *10*, 3853.
[97] S. A. Chechetka, Y. Yu, X. Zhen, M. Pramanik, K. Pu, E. Miyako, *Nat. Commun.* **2017**, *8*, 15432.
[98] Y. Lyu, C. Xie, S. A. Chechetka, E. Miyako, K. Pu, *J. Am. Chem. Soc.* **2016**, *138*, 9049.
[99] S. Yoo, S. Hong, Y. Choi, J.-H. Park, Y. Nam, *ACS Nano* **2014**, *8*, 8040.
[100] S. Yoo, R. Kim, J.-H. Park, Y. Nam, *ACS Nano* **2016**, *10*, 4274.
[101] J. W. Lee, H. Jung, H. H. Cho, J. H. Lee, Y. Nam, *Biomaterials* **2018**, *153*, 59.
[102] E. J. Gomez, K. Gerhardt, J. Judd, J. J. Tabor, J. Suh, *ACS Nano* **2015**, *10*, 225.
[103] S. A. Stanley, J. E. Gagner, S. Damanpour, M. Yoshida, J. S. Dordick, J. M. Friedman, *Science* **2012**, *336*, 604.
[104] K. Zhang, B. Cui, *Trends Biotechnol.* **2015**, *33*, 92.
[105] K. Watanabe, T. Ohtsuki, *Prog. Mol. Biol. Transl. Sci.* **2016**, *139*, 101.
[106] H. Ando, T. Furuta, R. Y. Tsien, H. Okamoto, *Nat. Genet.* **2001**, *28*, 317.
[107] L. He, Y. Zhang, G. Ma, P. Tan, Z. Li, S. Zang, X. Wu, J. Jing, S. Fang, L. Zhou, Y. Wang, Y. Huang, P. G. Hogan, G. Han, Y. Zhou, *Elife* **2015**, *4*, e10024.
[108] B. Zheng, H. Wang, H. Pan, C. Liang, W. Ji, L. Zhao, H. Chen, X. Gong, X. Wu, J. Chang, *ACS Nano* **2017**, *11*, 11898.
[109] G. G. Genchi, A. Marino, A. Grillone, I. Pezzini, G. Ciofani, *Adv. Healthcare Mater.* **2017**, *6*, 1700002.
[110] H.-w. Kim, K. Yang, W.-j. Jeong, S.-j. Choi, J. S. Lee, A.-N. Cho, G.-E. Chang, E. Cheong, S.-W. Cho, Y.-b. Lim, *ACS Appl. Mater. Interfaces* **2016**, *8*, 26470.
[111] A. Marino, S. Arai, Y. Hou, A. Degl'Innocenti, V. Cappello, B. Mazzolai, Y.-T. Chang, V. Mattoli, M. Suzuki, G. Ciofani, *ACS Nano* **2017**, *11*, 2494.
[112] Y. Lyu, D. Cui, H. Sun, Y. Miao, H. Duan, K. Pu, *Angew. Chem. Int. Ed.* **2017**, *56*, 9155.
[113] E. Miyako, T. Deguchi, Y. Nakajima, M. Yudasaka, Y. Hagihara, M. Horie, M. Shichiri, Y. Higuchi, F. Yamashita, M. Hashida, Y. Shigeri, Y. Yoshida, S. Lijima, *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 7523.
[114] Y. Wang, S. Li, P. Zhang, H. Bai, L. Feng, F. Lv, L. Liu, S. Wang, *Adv. Mater.* **2018**, *30*, 1705418.
[115] Y. Liu, G. Shu, X. Li, H. Chen, B. Zhang, H. Pan, T. Li, X. Gong, H. Wang, X. Wu, Y. Dou, J. Chang, *Adv. Funct. Mater.* **2018**, *28*, 1802026.
[116] S. P. Sanchez-Rodriguez, J. P. Sauer, S. A. Stanley, X. Qian, A. Gottesdiener, J. M. Friedman, J. S. Dordick, *Biotechnol. Bioeng.* **2016**, *113*, 2228.
[117] W. Gao, Y. Sun, M. Cai, Y. Zhao, W. Cao, Z. Liu, G. Cui, B. Tang, *Nat. Commun.* **2018**, *9*, 231.
[118] A. Ambrosone, V. Marchesano, S. Carregal-Romero, D. Intartaglia, W. J. Parak, C. Tortiglione, *ACS Nano* **2016**, *10*, 4828.
[119] R. A. Blidner, K. R. Svoboda, R. P. Hammer, W. T. Monroe, *Mol. BioSyst.* **2008**, *4*, 431.

[120] Y. Matsushita-Ishiodori, T. Ohtsuki, *Acc. Chem. Res.* **2012**, *45*, 1039.
[121] M. K. G. Jayakumar, N. M. Idris, Y. Zhang, *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 8483.
[122] J. Li, C. W. T. Leung, D. S. H. Wong, J. Xu, R. Li, Y. Zhao, C. Y. Y. Yung, E. Zhao, B. Z. Tang, L. Bian, *ACS Appl. Mater. Interfaces* **2017**, 10.1021/acsami.7b00845.
[123] M. K. G. Jayakumar, A. Bansal, K. Huang, R. Yao, B. N. Li, Y. Zhang, *ACS Nano* **2014**, *8*, 4848.
[124] M. K. G. Jayakumar, A. Bansal, B. N. Li, Y. Zhang, *Nanomedicine* **2015**, *10*, 1051.
[125] S. Ranjan, M. K. G. Jayakumar, Y. Zhang, *Nanomedicine* **2015**, *10*, 1477.
[126] W. Li, J. Wang, J. Ren, X. Qu, *J. Am. Chem. Soc.* **2014**, *136*, 2248.
[127] C. J. Carling, F. Nourmohammadian, J. C. Boyer, N. R. Branda, *Angew. Chem. Int. Ed.* **2010**, *49*, 3782.
[128] H. Kang, K. Zhang, D. S. H. Wong, F. Han, B. Li, L. Bian, *Biomaterials* **2018**, *178*, 681.
[129] H. Kang, K. Zhang, Q. Pan, S. Lin, D. S. H. Wong, J. Li, W. Y. W. Lee, B. Yang, F. Han, G. Li, B. Li, L. Bian, *Adv. Funct. Mater.* **2018**, *28*, 1802642.
[130] D. Ghezzi, M. R. Antognazza, R. Maccarone, S. Bellani, E. Lanzarini, N. Martino, M. Mete, G. Pertile, S. Bisti, G. Lanzani, *Nat. Photonics* **2013**, *7*, 400.
[131] J. F. Maya-Vetencourt, D. Ghezzi, M. R. Antognazza, E. Colombo, M. Mete, P. Feyen, A. Desii, A. Buschiazzo, M. Di Paolo, S. Di Marco, *Nat. Mater.* **2017**, *16*, 681.
[132] Y. Ma, J. Bao, Y. Zhang, Z. Li, X. Zhou, C. Wan, L. Huang, Y. Zhao, G. Han, T. Xue, *Cell* **2019**, *177*, 243.
[133] T. S. Johnson, A. C. O'Neill, P. M. Motarjem, C. Amann, T. Nguyen, M. A. Randolph, J. M. Winograd, I. E. Kochevar, R. W. Redmond, *J. Surg. Res.* **2007**, *143*, 224.
[134] S. J. Frost, D. Mawad, J. Hook, A. Lauto, *Adv. Healthcare Mater.* **2016**, *5*, 401.
[135] S. Han, B. W. Hwang, E. Y. Jeon, D. Jung, G. H. Lee, D. H. Keum, K. S. Kim, S. H. Yun, H. J. Cha, S. K. Hahn, *ACS Nano* **2017**, *11*, 9979.
[136] J. Li, H. Mao, N. Kawazoe, G. Chen, *Biomater. Sci.* **2017**, *5*, 173.
[137] H. Koo, M. S. Huh, I.-C. Sun, S. H. Yuk, K. Choi, K. Kim, I. C. Kwon, *Acc. Chem. Res.* **2011**, *44*, 1018.
[138] P. Cherukuri, E. S. Glazer, S. A. Curley, *Adv. Drug Delivery Rev.* **2010**, *62*, 339.
[139] R. R. Arvizo, S. Bhattacharyya, R. A. Kudgus, K. Giri, R. Bhattacharya, P. Mukherjee, *Chem. Soc. Rev.* **2012**, *41*, 2943.
[140] S. J. Soenen, P. Rivera-Gil, J.-M. Montenegro, W. J. Parak, S. C. De Smedt, K. Braeckmans, *Nano Today* **2011**, *6*, 446.
[141] N. Lee, S. H. Choi, T. Hyeon, *Adv. Mater.* **2013**, *25*, 2641.
[142] E. B. Ehlerding, F. Chen, W. Cai, *Adv. Sci.* **2016**, *3*, 1500223.
[143] S. Tang, C. Peng, J. Xu, B. Du, Q. Wang, R. D. Vinluan III, M. Yu, M. J. Kim, J. Zheng, *Angew. Chem. Int. Ed.* **2016**, *55*, 16039.
[144] G. Yang, L. Xu, Y. Chao, J. Xu, X. Sun, Y. Wu, R. Peng, Z. Liu, *Nat. Commun.* **2017**, *8*, 902.
[145] G. Hong, J. C. Lee, J. T. Robinson, U. Raaz, L. Xie, N. F. Huang, J. P. Cooke, H. Dai, *Nat. Med.* **2012**, *18*, 1841.
[146] J. Liu, M. Yu, C. Zhou, J. Zheng, *Mater. Today* **2013**, *16*, 477.
[147] C. Xie, X. Zhen, Q. Miao, Y. Lyu, K. Pu, *Adv. Mater.* **2018**, *30*, 1801331.
[148] X. Zhang, B. Li, X. Luo, W. Zhao, J. Jiang, C. Zhang, M. Gao, X. Chen, Y. Dong, *ACS Appl. Mater. Interfaces* **2017**, *9*, 25481.
[149] B. Xia, B. Wang, J. Shi, Y. Zhang, Q. Zhang, Z. Chen, J. Li, *Acta Biomater.* **2017**, *51*, 197.
[150] A. Bianco, K. Kostarelos, M. Prato, *Chem. Commun.* **2011**, *47*, 10182.
[151] P. Huang, Y. Chen, H. Lin, L. Yu, L. Zhang, L. Wang, Y. Zhu, J. Shi, *Biomaterials* **2017**, *125*, 23.

[152] Y. Chen, Q. Meng, M. Wu, S. Wang, P. Xu, H. Chen, Y. Li, L. Zhang, L. Wang, J. Shi, *J. Am. Chem. Soc.* **2014**, *136*, 16326.
[153] L. Yu, Y. Chen, M. Wu, X. Cai, H. Yao, L. Zhang, H. Chen, J. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 9881.
[154] Y. Lyu, J. Zeng, Y. Jiang, X. Zhen, T. Wang, S. Qiu, X. Lou, M. Gao, K. Pu, *ACS Nano* **2018**, *12*, 1801.
[155] C. Yin, X. Zhen, Q. Fan, W. Huang, K. Pu, *ACS Nano* **2017**, *11*, 4174.
[156] T. Lei, M. Guan, J. Liu, H.-C. Lin, R. Pfattner, L. Shaw, A. F. McGuire, T.-C. Huang, L. Shao, K.-T. Cheng, J. B.-H. Tok, Z. Bao, *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 5107.
[157] T. Repenko, A. Rix, S. Ludwanowski, D. Go, F. Kiessling, W. Lederle, A. J. Kuehne, *Nat. Commun.* **2017**, *8*, 470.
[158] L. Cheng, C. Wang, L. Feng, K. Yang, Z. Liu, *Chem. Rev.* **2014**, *114*, 10869.
[159] Y. Maruoka, T. Nagaya, K. Sato, F. Ogata, S. Okuyama, P. L. Choyke, H. Kobayashi, *Mol. Pharm.* **2018**, *15*, 3634.
[160] Y. Jiang, J. Li, X. Zhen, C. Xie, K. Pu, *Adv. Mater.* **2018**, *30*, 1705980.
[161] Y. Jiang, P. K. Upputuri, C. Xie, Z. Zeng, A. Sharma, X. Zhen, J. Li, J. Huang, M. Pramanik, K. Pu, *Adv. Mater.* **2019**, *31*, 1808166.
[162] L. Liu, S. Wang, B. Zhao, P. Pei, Y. Fan, X. Li, F. Zhang, *Angew. Chem. Int. Ed.* **2018**, *57*, 7518.
[163] H. Lin, S. Gao, C. Dai, Y. Chen, J. Shi, *J. Am. Chem. Soc.* **2017**, *139*, 16235.
[164] D. J. Garfield, N. J. Borys, S. M. Hamed, N. A. Torquato, C. A. Tajon, B. Tian, B. Shevitski, E. S. Barnard, Y. D. Suh, S. Aloni, *Nat. Photonics* **2018**, *12*, 402.
[165] Y. Lyu, Y. Fang, Q. Miao, X. Zhen, D. Ding, K. Pu, *ACS Nano* **2016**, *10*, 4472.
[166] J. Zhang, C. Yang, R. Zhang, R. Chen, Z. Zhang, W. Zhang, S. H. Peng, X. Chen, G. Liu, C. S. Hsu, *Adv. Funct. Mater.* **2017**, *27*, 1605094.
[167] R. Zheng, S. Wang, Y. Tian, X. Jiang, D. Fu, S. Shen, W. Yang, *ACS Appl. Mater. Interfaces* **2015**, *7*, 15876.
[168] S. Li, K. Chang, K. Sun, Y. Tang, N. Cui, Y. Wang, W. Qin, H. Xu, C. Wu, *ACS Appl. Mater. Interfaces* **2015**, *8*, 3624.
[169] L. Huang, Z. Li, Y. Zhao, J. Yang, Y. Yang, A. I. Pendharkar, Y. Zhang, S. Kelmar, L. Chen, W. Wu, J. Zhao, G. Han, *Adv. Mater.* **2017**, *29*, 1604789.
[170] W. Wu, D. Mao, F. Hu, S. Xu, C. Chen, C. J. Zhang, X. Cheng, Y. Yuan, D. Ding, D. Kong, *Adv. Mater.* **2017**, *29*, 1700548.
[171] M. Zhang, Z. Cui, R. Song, B. Lv, Z. Tang, X. Meng, X. Chen, X. Zheng, J. Zhang, Z. Yao, W. Bu, *Biomaterials* **2018**, *155*, 135.
[172] C. Wang, Q. Zhang, X. Wang, H. Chang, S. Zhang, Y. Tang, J. Xu, R. Qi, Y. Cheng, *Angew. Chem. Int. Ed.* **2017**, *56*, 6767.
[173] Y. Lyu, J. Tian, J. Li, P. Chen, K. Pu, *Angew. Chem. Int. Ed.* **2018**, *57*, 13484.
[174] H.-D. Gao, P. Thanasekaran, C.-W. Chiang, J.-L. Hong, Y.-C. Liu, Y.-H. Chang, H.-M. Lee, *ACS Nano* **2015**, *9*, 7041.
[175] Q. Pei, X. Hu, X. Zheng, S. Liu, Y. Li, X. Jing, Z. Xie, *ACS Nano* **2018**, *12*, 1630.
[176] Y. Yuan, J. Liu, B. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 7163.
[177] L. Zhao, J. Peng, Q. Huang, C. Li, M. Chen, Y. Sun, Q. Lin, L. Zhu, F. Li, *Adv. Funct. Mater.* **2014**, *24*, 363.
[178] L. Huang, Y. Zhao, H. Zhang, K. Huang, J. Yang, G. Han, *Angew. Chem. Int. Ed.* **2017**, *56*, 14400.
[179] H. C. Huang, M. Pigula, Y. Fang, T. Hasan, *Small* **2018**, *14*, 1800236.
[180] K. Sano, T. Nakajima, P. L. Choyke, H. Kobayashi, *ACS Nano* **2012**, *7*, 717.
[181] Y. Mir, S. A. Elrington, T. Hasan, *Nanomedicine* **2013**, *9*, 1114.

The table of contents

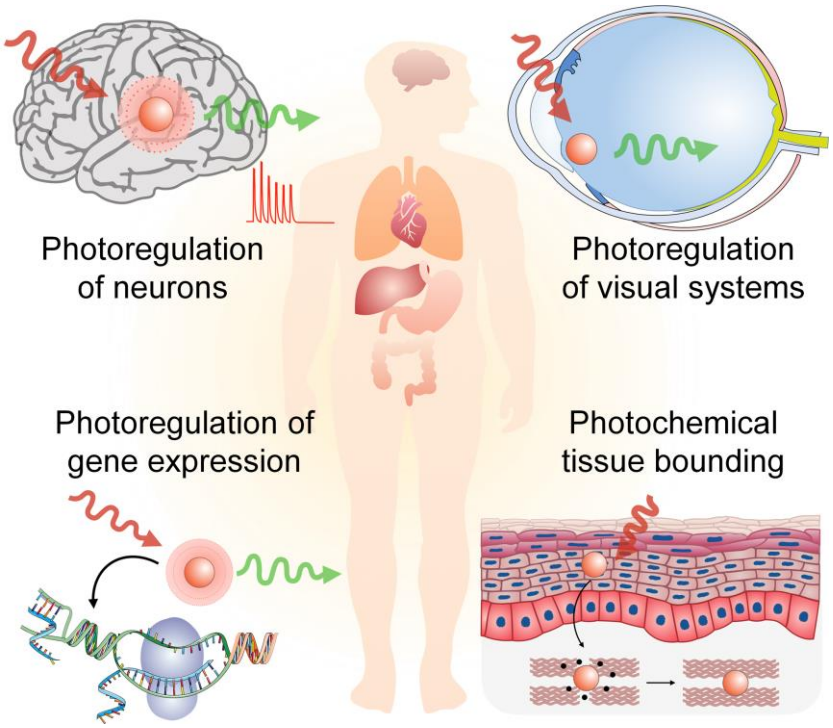
Near-infrared (NIR) photoregulation provides a promising approach for remote control of biological events and innovation of new therapeutic modalities. This progress report summarizes the recent development of optical nanotransducers for NIR photoregulation applications including photoregulation of neural activity, gene expression, and visual systems, as well as photochemical tissue bonding.

Keyword: Nanotransducers; photoregulation; near-infrared light; nanoparticles; biomedicine

Authors: J. Li, H. Duan, and K. Pu*

Nanotransducers for Near-Infrared Photoregulation in Biomedicine

ToC figure



Jingchao Li received his PhD degree in Materials Science and Engineering from the University of Tsukuba (Japan) in 2017. Then he worked as a Postdoctoral Research Fellow at Prof. Kanyi Pu's group in the School of Chemical and Biomedical Engineering (SCBE), Nanyang Technological University (NTU). His current research focuses on the development of advanced optical agents for cancer theranostics and biological photoregulation.

Hongwei Duan received his B.S. in applied chemistry and M.S. in polymer chemistry & physics at Fudan University. After completing his Ph.D. with Prof. Helmuth Möhwald at the Max Planck Institute of Colloids and Interfaces, he had his postdoctoral training with Prof. Shuming Nie in the joint Department of Biomedical Engineering at Emory University and Georgia Institute of Technology. He joined the School of Chemical and Biomedical Engineering (SCBE) at Nanyang Technological University (NTU) as an Assistant Professor in 2009. His current research focuses on developing new chemistry towards nanostructures with structurally integrated inorganic nanocrystals and polymers and new approaches towards well-defined multifunctional assemblies of nanoscale building blocks and exploring the emerging optical, electronic, magnetic, catalytic, and structural properties of these materials for biomedical and environmental applications.

Kanyi Pu received his PhD from the National University of Singapore in 2011 followed by a postdoctoral study at Stanford University School of Medicine. He joined the School of Chemical and Biomedical Engineering (SCBE) at Nanyang Technological University (NTU) as an Associate Professor in 2015. His research lies at the intersection of chemistry, nanotechnology, biophotonics and medicine, aiming to develop smart molecular probes and advanced imaging technologies to understand, detect and treat life-threatening diseases.