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Noninvasive Manipulation of Ion Channels for Neuromodulation and Theranostics

Yuxia Liu, Zhigao Yi, Yun Yao, Bing Guo, and Xiaogang Liu*

Cite This: *Acc. Mater. Res.* 2022, 3, 247−258

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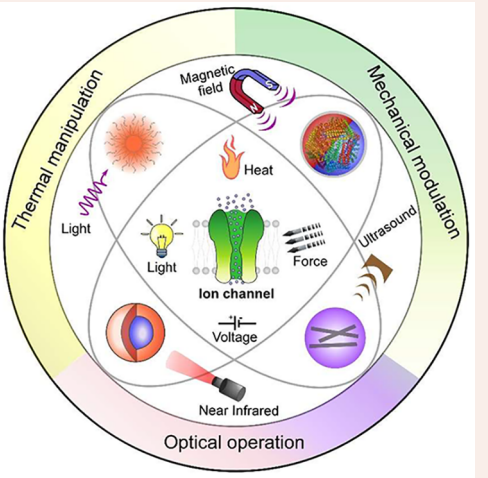
CONSPECTUS: Functional and structural studies of ion channels have deepened our understanding of their mechanisms and important role in regulating neuronal activity and treating disease. Manipulation of ion channels can directly control electrochemical signals in the nervous and cardiovascular systems for advanced neuromodulation and theranostics. Manipulation tools based on ion channel control, such as optogenetics, electrical stimulation, chemogenetics, and gene editing, have advanced basic biomedical research and enabled unprecedented treatment strategies. Nevertheless, conventional approaches are associated with limitations such as invasiveness, irreversibility, or low spatiotemporal resolution, which limit their clinical application. Therefore, targeted noninvasive or minimally invasive modulation of various ion channel activities is highly desirable.



In recent years, nanomaterials have enabled noninvasive and precise modulation of ion channels due to their tunable morphology and physicochemical properties. Based on activation modes, current nanomaterial-based methods for ion channel control include light stimulation, thermal regulation, and mechanical manipulation. Nanomaterials can serve as energy transducers to convert macroscopic signals that penetrate deep into tissue, such as near-infrared light or magnetic fields, into local stimuli for ion channel manipulation. For photomodulation, lanthanide-doped nanoparticles convert near-infrared light into visible energy by upconversion, enabling bidirectional control of excitatory and inhibitory opsins in deep tissues. For thermal modulation, photothermal nanoparticles transform absorbed light, such as near-infrared, into heat to activate thermosensitive channels in deep targets. For mechanical manipulation, magnetic nanoparticles convert external magnetic fields into local attractive and torque forces to regulate the functionality of mechanosensitive channels without concern for penetration depth. Moreover, nanomaterial-based strategies can realize targeted and minimally invasive control over the activities of various ion channels even at the single-cell level, maximizing their feasibility and application potential.

In this Account, we focus on the manipulation of ion channels using nanomaterials and categorize current approaches into photoconversion optogenetics, thermogenetics, and magnetogenetics. We first introduce the biological principles of various opsins, discuss thermo- and mechanosensitive ion channels and describe their molecular mechanisms in the context of channel structures. We also outline the general principles of emerging nanomaterials in terms of energy conversion capability. We highlight the major advances in nanoprobe-enabled systems and their modern applications in neuromodulation and theranostics. We conclude the Account with a discussion of existing challenges and future prospects.

1. INTRODUCTION

Ion channels form the molecular basis of bioelectricity. They establish resting membrane potentials, balance electrostatic charges, and maintain ion homeostasis in the cell membrane.[1] Dysfunction of ion channels has been associated with numerous diseases, including neurodegenerative, cardiovascular, renal, and pulmonary diseases.[1] Remote and selective modulation of ion channel activities is important for the study of physiological mechanisms and for the development of precision therapies. To date, several strategies such as chemogenetics, electrical stimulation, gene editing, and optogenetics have been developed to achieve in vivo control over specific ion channels. However, each approach faces its own major obstacles.[2] Chemogenetics is limited by its low spatiotemporal resolution and the potential toxicity of chemical drugs. Electrical stimulation is restricted by invasive implantation of electrodes, low cell specificity, and unclear mechanisms. Gene editing is constrained by its irreversibility,

Received: November 12, 2021
Revised: December 22, 2021
Published: January 14, 2022

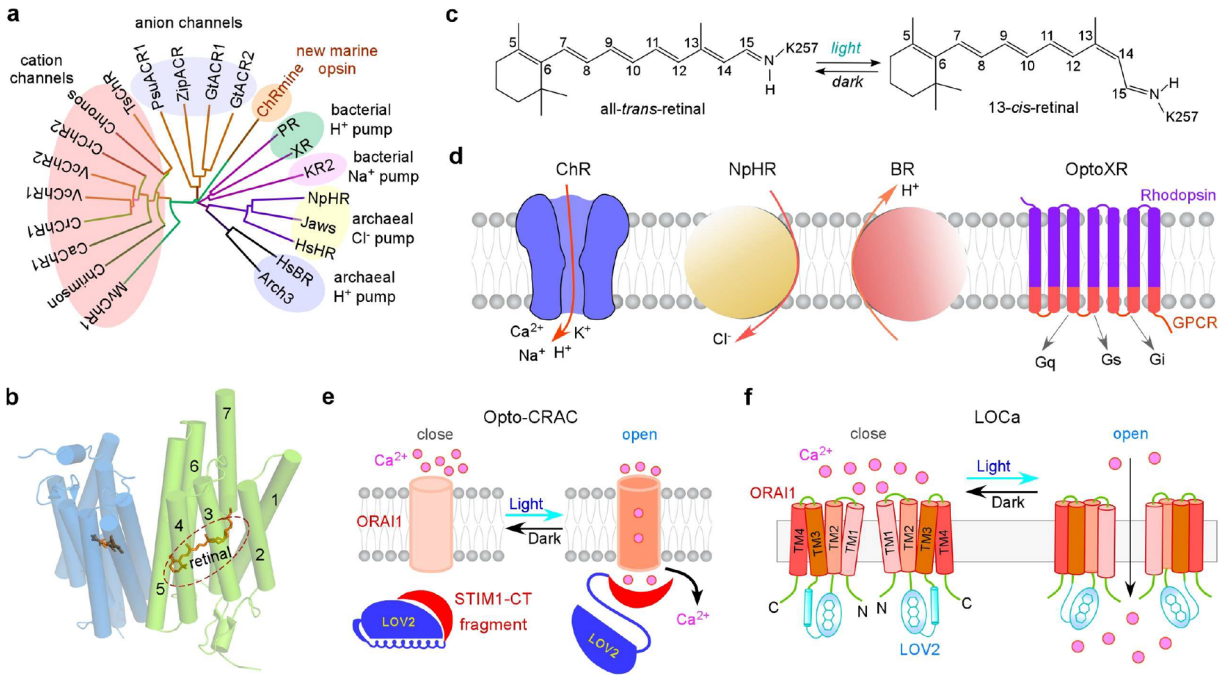


Figure 1. Principles of optogenetic methods. (a) Classification of opsin genes. (b) Structure of representative opsin ChR2 (PDB: 6EID). (c) Light-induced transformation of retinal. (d) Working mechanisms of ChR, NpHR, BR, and OptoXR. (e) Schematic description of opto-CRAC. (f) Schematic depiction of LOCa. Adapted with permission from: ref 3, copyright 2019 The American Association for the Advancement of Science; ref 11, copyright 2015 eLife Sciences Publications Ltd.; ref 12, copyright 2021 Springer Nature.

resulting in poor temporal resolution. Optogenetics, which uses light to stimulate genetically modified neurons by modulating their ion channels, has revolutionized neuroscience research because of its outstanding advantages in spatiotemporal resolution, reversible on−off controllability, cell-type specificity, and low toxicity.[3] However, conventional optogenetics involves visible spectrum illumination, which limits tissue penetration depth. Hence, surgical implantation of optical fibers is required to deliver light to deep-seated regions, which in turn leads to infection and irreversible tissue damage. To address these issues, reliable techniques with high spatiotemporal precision and minimal invasiveness are highly desirable.

Owing to the convergence between nanomaterials and ion channels at the nanoscale, functional nanomaterials have been used for targeted temporal control of ion channels. A plethora of nanomaterials, such as lanthanide-doped upconversion nanoprobes, photothermal nanomaterials, and magnetic nanoparticles, have been utilized to develop alternative approaches to control ion channel activities in vivo. Using nanoparticles as nanoscale energy transducers, near-infrared (NIR) light and magnetic fields can be converted into local physiological stimulation of specific ion channels, allowing remote control of cellular functions and behaviors in deep tissues.[4,5] Additionally, nanomaterials can be delivered into the body in a variety of convenient ways without the need for complex surgery, thus avoiding tissue damage. Furthermore, nanotechnology offers excellent specificity and selectivity due to a wide range of surface modification methods.[6] Altogether, nanotechnology-based modulation approaches offer high sensitivity, superior spatiotemporal resolution, and minimal invasiveness, promising to facilitate basic and translational research and ultimately clinical treatment.

2. PHOTOCONVERSION MANIPULATION OF LIGHT-SENSITIVE ION CHANNELS

2.1. Light-Sensitive Ion Channels and Optogenetics

Optogenetics combines genetic engineering and optical manipulation to enable precise control of biological events in specific cell types in real time. Optogenetics uses exogenously expressed, light-sensitive ion channels or ion pumps to either activate or inhibit certain physiological processes under illumination at a particular wavelength. To conduct optogenetic experiments, three key factors must be considered: selection of appropriate opsins, efficient and specific expression of opsin genes within defined regions, and effective illumination. Currently, several opsin species have been discovered or developed and can be broadly classified as ion channels (e.g., cation and anion channels) and ion pumps (e.g., H^+, Cl^-, Na^+ pumps) (Figure 1a).[3] In general, rhodopsins are dimers and each monomer comprises seven transmembrane α-helices (Figure 1b).[7] Rhodopsins usually contain retinal as a chromophore for light absorption. Upon excitation, isomerization of the retinal from the *all-trans*-state to the 13-*cis*-state leads to activation of the protein (Figure 1c). Among various rhodopsins, channelrhodopsins (ChRs) are the most commonly used to mediate the influx of cations (Na^+, K^+, Ca^{2+}, and H^+) into cells, trigger depolarization, elicit action potentials, and perform excitatory functions (Figure 1d).[8] In contrast, bacteriorhodopsins (BRs) pump hydrogen ions out of cells and halorhodopsins (NpHRs) allow chloride ions to enter cells (Figure 1d). Hence, both BRs and NpHRs can elicit hyperpolarization to block action potentials, causing inhibitory effects. In addition, a new type of opsin-receptor chimeras, called OptoXR, has been developed to control G-protein-related signaling (Gq/Gs/Gi) via illumination (Figure 1d).[9] Various opsin mutants have been constructed to optimize

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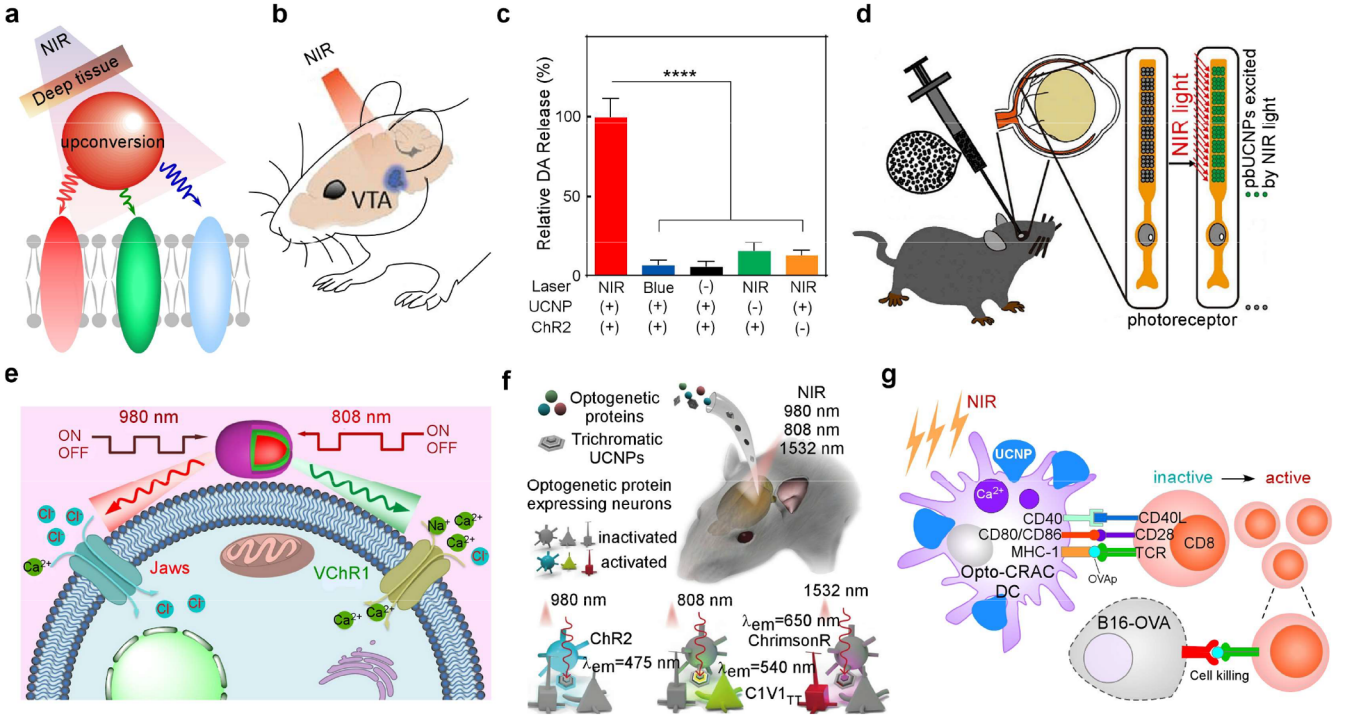

Figure 2. Upconversion-assisted optogenetics in a wireless manner. (a) Principles of UCNP-assisted optogenetics. (b) Schematic of the experimental procedure of UNCP-mediated optogenetics. (c) Relative dopamine (DA) release in the VTA under different conditions. (d) Depiction of NIR vision enabled by UCNPs. (e) Bidirectional modulation of both excitatory VChR1 and inhibitory Jaws. (f) NIR-excited trichromatic upconversion-mediated multicolor optogenetics. (g) Melanoma therapy by UCNP-mediated Opto-CRAC. Adapted with permission from: ref 4, copyright 2018 The American Association for the Advancement of Science; ref 17, copyright 2019 Elsevier; ref 18, copyright 2019 Springer Nature; ref 19, copyright 2021 Springer Nature; ref 11, copyright 2015 eLife Sciences Publications Ltd.

photon-sensitivity, ion conductance, and color-responsiveness. Recently, a red-shifted ChR (ChRmine) with a strong photocurrent was discovered and adopted for implant-free deep brain stimulation. However, the phototoxicity of the necessarily high irradiance (≥200 mW/mm^2) has yet to be overcome.[3,10]

Apart from opsin-based optogenetics, innovative light-guided platforms based on light-dependent modules and Ca^{2+}-selective ion channels have been developed to expand the optogenetics toolbox. Calcium release-activated calcium channel (CRAC) is a highly Ca^{2+}-selective channel comprising a pore-forming ORAI protein at the plasma membrane and a stromal interaction molecule (STIM) at the endoplasmic reticulum for luminal Ca^{2+} recognition. In principle, Ca^{2+} depletion in the reticulum initiates oligomerization and triggers subsequent conformational changes in the STIM that eventually lead to activation of ORAI and Ca^{2+} influx. On this basis, He et al.[11] engineered a light-driven platform, which they named Opto-CRAC, by constructing the LOV2-$STIM1_{336-486}$ chimera in which $STIM1_{336-486}$ is sufficient to activate ORAI (Figure 1e). In this system, $STIM1_{336-486}$ is maintained in an inactive state in the dark. Upon illumination, the conformational change of LOV2 activates $STIM1_{336-486}$ and ORAI to support Ca^{2+} influx (Figure 1e). Recently, a light-operated Ca^{2+} channel (LOCa) system was designed by inserting a LOV2 module into the intracellular loop of the engineered ORAI1 channel (Figure 1f).[12] LOCa can mediate light-induced Ca^{2+} influx without other cofactors, further simplifying the operation of Ca^{2+}-specific optogenetics. Ca^{2+}, as a versatile second messenger, is involved in vital physiological processes ranging from short-term neurotransmitter release to long-term development. Therefore, CRAC-based optogenetics provides a complementary tool to exquisitely regulate Ca^{2+} flux without interference from other ions such as Na^+ and K^+, which is unattainable with low-specificity opsin systems.

Despite the revolutionary role of optogenetics, the wavelength of peak excitation of current opsins is limited to the visible spectrum. Given the shallow penetration depth (~1 mm) of visible light into tissue, excitation light is usually transmitted via surgically implanted optical fibers, which can cause side effects such as tissue damage, infection, and inflammation. Moreover, wired fibers can lead to numerous inconveniences, including restricted motion, artifacts, and unstable signals due to frequent fiber displacement. Since the intensity of light scattering is proportional to $1/\lambda^4$, long-wavelength NIR light has proven effective in overcoming the trade-offs between stimulation depth and efficiency.

2.2. Upconversion Nanoparticles

Although NIR-activated opsins have not yet been developed, photon upconversion offers an alternative solution. We and others have devoted substantial efforts to lanthanide-doped upconversion nanoparticles (UCNPs) which can convert NIR excitation into shorter-wavelength emission and also exhibit other useful properties, such as exceptional photostability and extremely low autofluorescence.[13] UCNPs typically consist of a host lattice with low phonon energy, a special type of sensitizer for NIR harvesting, and low-concentration activators that extract excitation energy from the sensitizer. Lanthanide ions such as Er^{3+}, Tm^{3+}, or Ho^{3+} are often used as activators. Yb^{3+} is often used as a sensitizer because its absorption band matches

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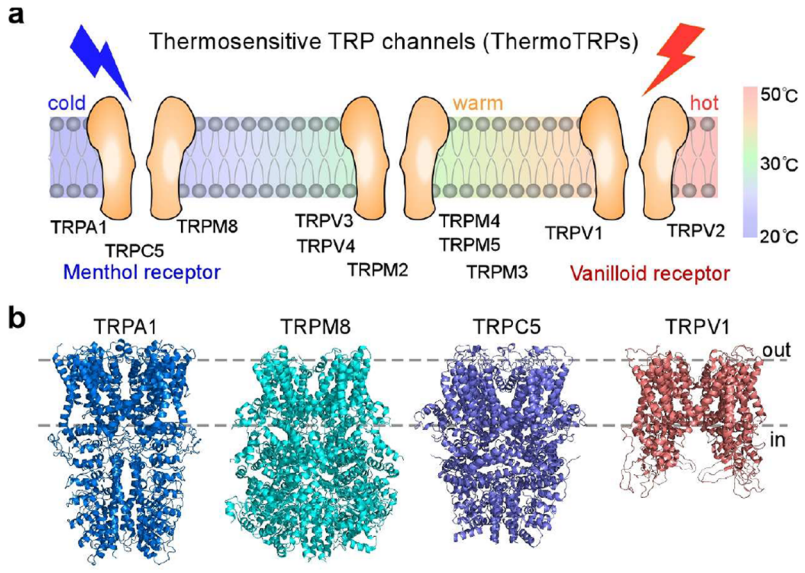

Figure 3. Temperature responsiveness and structural architecture of representative thermoTRPs. (a) Schematic illustration of temperature dependence of thermoTRPs. (b) Structures of representative thermoTRPs (channel [PDB]: TRPV1 [5IRZ], TRPM8 [6O6A], TRPC5 [6AEI], TRPV1 [5IRZ]).

the excitation of 980 nm diode lasers. Since water has strong absorption at 980 nm, the resulting overheating is a major problem for biological systems. Alternatively, Nd^{3+} with peak absorption at ∼800 nm can be used to mitigate the overheating. Furthermore, the emission colors of UCNPs can be tuned from ultraviolet to visible by controlling the particle size, dopant concentration, and particle composition.[6] Notably, surface modification or functionalization of UCNPs is generally required to improve targetability, photostability, water solubility, and biocompatibility. By combining the advantages of optogenetics and UCNPs, a number of UCNP-assisted techniques have been developed to enable remote and minimally invasive optogenetics (Figure 2a).[14]

2.3. Upconversion-Mediated Optogenetics

The first attempt at UCNP-mediated optogenetics was performed at the cellular level. Blue-emitting $NaYF_4$:Yb/Tm UCNPs were first encapsulated in an organic scaffold to activate cultured ChR2-expressing neurons and elicit action potentials.[15] We extended UCNP-mediated optogenetics to mammalian systems using $NaYF_4$:Yb/Tm@SiO_2 nanoparticles.[4] These core−shell UCNPs were injected into the ventral tegmental area (VTA, ∼4.5 mm deep), where ChR2 was expressed (Figure 2b). Subsequently, transcranial pulsed NIR irradiation activated dopamine neurons, as confirmed by evoked neuronal spikes, increased expression of c-Fos (an indicator of neuronal activation), and increased dopamine release (Figure 2c). Apart from activation, UCNPs can effectively inhibit neuronal activity or intracellular signaling pathways by combining them with inhibitory opsins, NpHR and Arch. Moreover, UCNPs exhibit long-term stability and low dispersion in deep neuronal tissues, circumventing potential background interference from nonspecific diffusion. Recently, Miyazaki et al.[16] further illustrated the long-term applicability (>8 weeks) of UCNP-mediated optogenetics to manipulate locomotion in mice under freely moving conditions. Besides exogenous transgenic opsins, native retinal opsins can also be stimulated using UCNPs to provide NIR vision to mice (Figure 2d).[17]

Previously developed optogenetic NIR methods can only be activated or inhibited using two different sets of nanoparticles. Recently, Mei et al.[18] synthesized Er^{3+}/Tm^{3+}-sensitized, orthogonally tunable UCNPs that showed green or red emission upon excitation of 808 or 980 nm, respectively (Figure 2e). These nanoparticles could activate VChR1 or Jaws to elicit depolarization or hyperpolarization in the same cells. In addition, Liu et al.[19] recently developed trichromatic UCNP-mediated multicolor optogenetics with blue, green, and red emission to activate ChR2, C1V1, and ChrimsonR, respectively (Figure 2f). Such a multiplexed system could selectively activate different neuron populations to simultaneously modulate different rodent locomotion behaviors. In addition to opsin-based upconversion optogenetics, He et al.[11] reported remote NIR photoactivation of Opto-CRAC by blue-emitting $NaYF_4$:Yb/Tm@$NaYF_4$ nanoparticles. Using this system, irradiation at 980 nm induced a series of Ca^{2+}-mediated events such as translocation of nuclear factor of activated T cells and dendritic cell-mediated immunotherapy (Figure 2g). Since Ca^{2+} overload is lethal to cells, remote manipulation of Ca^{2+}-specific Opto-CRAC systems is suitable for various antitumor therapies. In addition to neuromodulation and tumor treatment, UCNP can also serve as an excellent nanotracer for biological entities due to its outstanding luminescence stability. Recently, we developed a real-time cargo tracking system for sensory neurons using upconversion nanoprobes, showing promise for the diagnosis of neurodegenerative disorders.[20] On the basis of this upconversion microscopy system, we have developed an in situ neuropathy assessment platform for drug screening.[21]

In particular, UCNP-mediated optogenetic techniques described above eliminate the need for fiber optical implantation surgeries without compromising the depth of tissue penetration for visible light transmission, greatly simplifying the overall operation.

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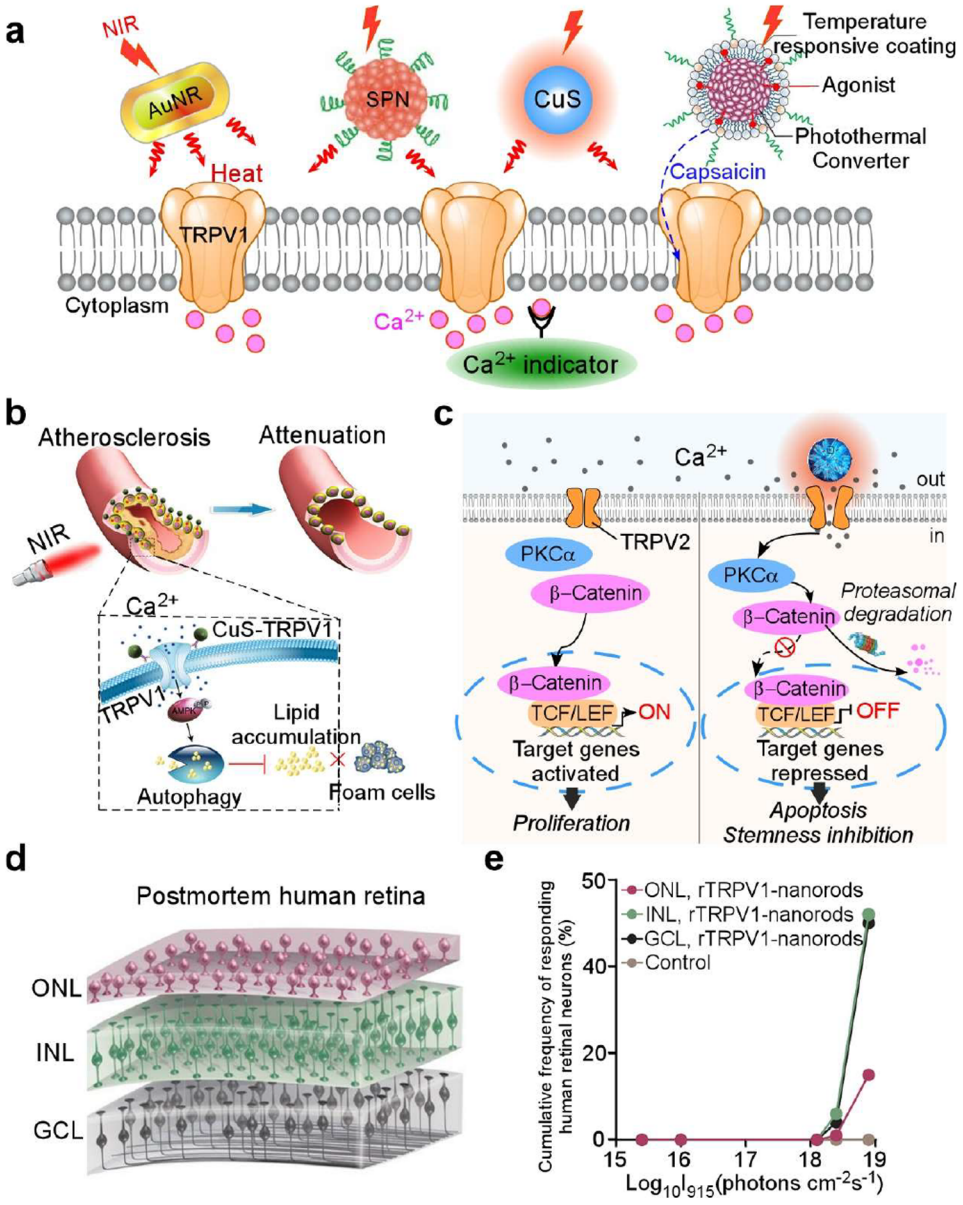

Figure 4. Applications of photothermogenetics. (a) Schematic summary of different photothermic modulation approaches for TRPV1. (b) Schematic description of CuS-assisted photothermal treatment of atherosclerosis. (c) Proposed mechanism for cancer therapy using the TRPV2-PCNH system. (d) Schematic of the retinal layers of a post-mortem human. (e) Cumulative frequency of responding neurons in different retinal layers. Adapted with permission from: ref 28, copyright 2018 Springer Nature; ref 31, copyright 2020 Springer Nature; ref 32, copyright 2020 The American Association for the Advancement of Science.

3. PHOTOTHERMAL MANIPULATION OF THERMOSENSITIVE ION CHANNELS

3.1. Thermosensitive Ion Channels

Apart from light, temperature is another important stimulus that modulates ion channel activities. Temperature-sensitive ion channels are composed of several individual proteins and are essential for maintaining thermal homeostasis in the body. Several members of the transient receptor potential (TRP) family, including TRPV1-V4, TRPM8, and TRPA1, have been confirmed to behave in a temperature-dependent manner and are therefore commonly referred to thermoTRPs. ThermoTRPs are considered peripheral heat sensors that cover a wide range of temperatures (Figure 3a). TRP channels constitute a group of channels that form cation-permeable pores. TRPs are generally activated by thermal, mechanical, and chemical stimuli. They are also involved in other sensory modalities, including chemosensation, mechanosensation, phototransduction, and nociception.[22] In recent years, high-resolution structures of almost all TRP channels have been reported. They share the structural features of four subunits and each of them contains six transmembrane segments (TM1−TM6), with TM1−TM4 and TM5 and TM6 serving as the voltage-sensitive and pore domains, respectively (Figure 3b).[23] Despite the structural similarities, the universal gating mechanisms of TRPs remain elusive, in part because of the complicated interaction sites as well as the modes of action of different stimuli. For example, the mechanism of thermal activation is difficult to determine because heat diffuses easily and is rarely directly to a specific site. It is also difficult to

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Acc. Mater. Res. 2022, 3, 247−258

manipulate thermodynamic processes in situ. Hence, in vivo thermal studies using conventional methods such as heating or cooling perfusion are not possible, let alone remote control with high spatiotemporal resolution. Therefore, localized heating tools could provide valuable opportunities to improve the current dilemma of remote thermal modulation of specific ion channels.

3.2. Photothermal Nanomaterials

Localized heating can be achieved through photothermal effects mediated by photothermal nanomaterials that convert absorbed light into thermal energy through nonradiative relaxation. In recent years, superior photothermal conversion efficiency has been reported when NIR is used as a radiation source. Moreover, a variety of photothermal materials have been utilized, including noble metals, carbon-based nanomaterials, semiconductor nanomaterials, black phosphorus, and semiconducting polymers. Different materials have different photothermal conversion properties. Gold nanoparticles (AuNPs), for example, use surface plasmon resonance (SPR) to convert photon energy into heat. Since surface features such as shape or size can influence the SPR effect, gold nanorods (AuNRs) have been designed to shift SPR from the visible to the NIR region. Similar to AuNPs, carbon-based nanomaterials, such as nanotubes and graphene, also rely on the SPR effect to convert light into heat. CuS nanoparticles can be photoexcited via the d−d transition of Cu^{2+}, which tolerates changes in the environment.[24] Another emerging class of photothermal nanomaterials are semiconducting polymer nanomaterials with excellent biocompatibility and size-independent optical characteristics. The light-inducible thermal effect of semiconducting polymer nanomaterials is mainly achieved by nonradiative relaxation in the excited state via the donor−acceptor backbone.[25] Photothermal nanoparticles hold great promise for therapy, and substantial effort has been made to synthesize and use them for the manipulation of ion channels, gene carriers, and nanoenzymes.

3.3. Photothermal Nanomaterial-Mediated Thermogenetics

Vanilloid receptor1 (TRPV1), a type of thermoTRPs, is useful to detect noxious chemical and thermal stimuli. TRPV1 can be activated by polymodal stimuli such as capsaicin, pH (<5.2), resiniferatoxin, and heat (>43 °C).[22] After activation, TRPV1-mediated Ca^{2+} influx triggers various downstream signaling processes, including inflammatory hyperalgesia, pain, and bladder distension sensation.

In 2015, Nakatsuji et al.[26] showed that AuNRs can be coated with cationized high-density lipoproteins to target cell membranes. These AuNRs convert NIR to heat, which subsequently activates TRPV1 and elicits Ca^{2+} influx, as verified in cocultured dorsal root ganglion (DRG) neurons (Figure 4a). Thereafter, photothermal modulation of ion channels was extended to in vivo animal models for therapeutics. Because TRPV1 can induce autophagy to protect vascular smooth muscle cells from foam cell formation,[27] Gao et al.[28] coupled CuS nanoparticles with TRPV1 antibodies to specifically activate TRPV1 in an attempt to alleviate atherosclerosis (Figure 4b). The strategy of using heat instead of capsaicin to alleviate atherosclerosis avoids the chronic toxicity of capsaicin. In another study by Ma et al.,[29] a nanoplatform composed of CuS@$CaCO_3$-PEG and Ca^{2+}-permeable TRPV1 was created to artificially control Ca^{2+} overloaded stress for tumor treatment. Once the nanoparticles arrive at the tumor sites, the acidic microenvironment degrades $CaCO_3$ and releases CuS nanoparticles near the tumors. The NIR irradiation is then converted into heat by CuS nanoparticles, activating TRPV1 and subsequently inducing Ca^{2+} overload that kills tumor cells. Using a similar strategy, we recently exploited pH-sensitive calcium peroxide nanoparticles to control the dual-mode release of Ca^{2+} and hydrogen peroxide in tumors.[30] Accumulation of these signaling molecules led to the dysfunction of multiple ion channels and resulted in severe Ca^{2+} overload stress that killed tumor cells. In addition to TRPV1, vanilloid receptor 2 (TRPV2) is also a molecular target for photothermal modulation (Figure 3a). To activate TRPV2 and elicit Ca^{2+} influx, Yu et al.[31] exploited photothermal carbon nanohorns and NIR-II irradiation at 1064 nm (Figure 4c). This strategy effectively regulated downstream signaling pathways and attenuated cancer stemness. Photothermal nanosystems also hold promise for vision restoration. Nelidova et al.[32] recently developed a NIR sensor composed of AuNRs and modified TRPV1 (with 6 × His in the extracellular loop). This sensor activated cone receptors and elicited a response under NIR irradiation. The efficacy and feasibility of this sensor were validated in the post-mortem human retina. Because NIR light can penetrate deep into the tissue, this study provides a new paradigm for developing treatments for retinal and other ocular diseases (Figure 4d,e). Apart from direct thermal activation, Zhen et al.[33] created a photothermal-responsive nanoagonist to activate TRPV1. Capsaicin was encapsulated with semiconducting polymer nanomaterials and temperature-dependent 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) for photothermal ablation. Upon NIR irradiation, the released capsaicin activated TRPV1, resulting in Ca^{2+} overload and cell apoptosis.

Compared to optogenetics, which requires gene transfection into host cells, photothermogenetics does not require prior transgenesis in most cases because thermosensitive channels in mammalian systems are usually endogenous proteins. This feature allows specific cell stimulation and facilitates the development of innovative therapeutic approaches to modulate cells remotely. Moreover, the efficiency of photothermal conversion is usually much higher than that of photon upconversion. Therefore, photothermogenetics serves as a complementary modulatory approach alongside conventional optogenetics.

4. MAGNETIC MANIPULATION OF THERMOSENSITIVE AND MECHANOSENSITIVE ION CHANNELS

The effectiveness of optogenetics and photothermogenetics in mediating neuromodulation depends largely on illumination. However, light penetration into biological tissue is limited to the millimeter range. Due to the weak interactions between magnetic fields and biological molecules, peripheral magnetic stimulation penetrates deep into tissue without energy attenuation and without the need for mechanical contact. This provides a safe, effective, and noninvasive approach for manipulation of thermosensitive and mechanosensitive ion channels.

4.1. Magnetic Nanoparticles

As magnetic fields penetrate deep into cells and are noninvasive, a number of nanosystems based on magnetic nanoparticles as transducers have been exploited to control cellular events. For example, Fe_3O_4 and γ-Fe_2O_3 nanoparticles

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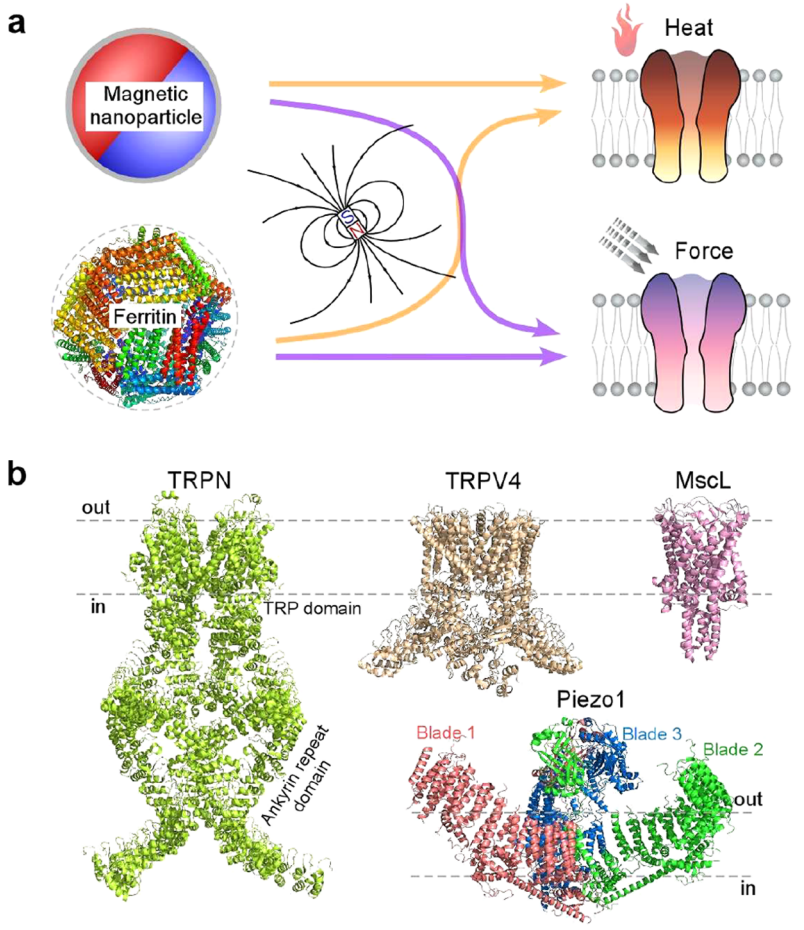

Figure 5. Magnetic manipulation of thermosensitive and mechanosensitive ion channels. (a) Modes of manipulation by magnetic signals. (b) Structures of representative mechanosensitive channels (protein [PDB]: ferritin [3RBC], TRPN [5VKQ], TRPV4 [6BBJ], MscL [2OAR], and Piezo1 [5Z10]).

have been used to convert macroscopic magnetic energy into local heat or mechanical force (Figure 5a). Thermal effects are mainly generated by hysteretic power loss, which refers to the energy consumption of ferromagnets due to hysteresis during repeated magnetization. Mechanical effects, on the other hand, can be produced in two routes: first, by a torque force parallel to the magnetic field, and second, by translational attraction. Under a given magnetic field, the properties of magnetic nanoparticles such as size, composition, shape, and surface chemistry are key factors affecting both thermal and mechanical effects. Commonly used magnetic materials include iron oxides (Fe_3O_4, Fe_2O_3), ferromagnetic metals (Fe, Co, Ni), and spinel-type metal oxides ($CoFe_2O_4$, $NiFe_2O_4$). Among them, Fe_3O_4 and γ-Fe_2O_3 are most frequently used for the synthesis of iron oxide nanoparticles. Due to their excellent biocompatibility and biodegradability, iron oxide nanoparticles have been adopted for a wide range of biomedical applications, including drug delivery, gene therapy, hyperthermia, magnetic resonance imaging, and cell separation.[34] Intriguingly, ferritin, a genetically encoded magnetic protein, has also been extensively studied in biological systems. Ferritin has a spherical shell-like crystalline structure, with iron embedded in its 5−12 nm core to detect applied magnetic fields (Figure 5a).[35] Inspired by optogenetics, magnetic nanoparticles and ferritin have also been harnessed to control the activities of ion channels and influence biological behaviors with high precision.

4.2. Mechanosensitive Ion Channels

Since a magnetic field can produce both thermal and mechanical effects, two main categories of ion channels that have been targeted are those associated with thermosensitive and mechanosensitive functions (Figure 5a). As thermosensitive channels have already been described in section 3.1, we focus on mechanosensitive channels in this section.

Mechanosensitive channels are susceptible to mechanical deformations of cell membranes and they contribute to both conscious sensations (touch and hearing) and unconscious sensations (blood flow). To date, several mechanosensitive channels have been identified, including Piezo1/2, TMC1/2, TREK/TRAAK K_{2P} channels, TMEM63/OSCA, and TRP channels (TRPN/NompC, TRPV4, TRPA1, TRPP2/3, etc.). Depending on whether additional auxiliaries are required, mechano-gating mechanisms have been proposed as membrane tension or tether models. In the membrane tension model, a force is applied to the membrane to open the channels, whereas in the tether model, the force is transmitted to the channel via binding to the extracellular matrix or cytoskeleton. Mechanosensitive channels perform mechanoresponsive behaviors via different structural modules. The bona fide mechanosensitive Piezo1 is a homotrimer with a propeller blade geometry (Figure 5b). The blade absorbs the force and

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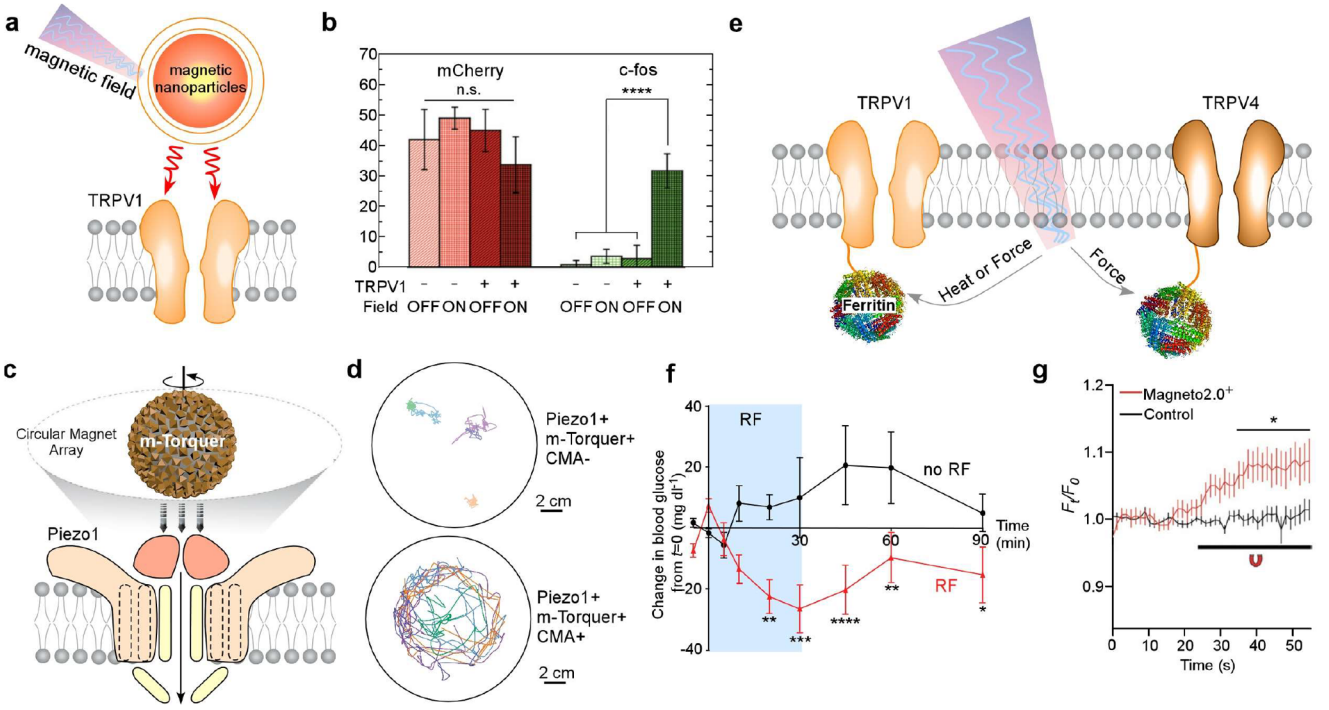

Figure 6. Applications of magnetogenetics. (a) Illustration of magnetic nanoparticle-mediated magnetothermal modulation of TRPV1. (b) Enhancement of c-Fos expression by magnetothermogenetics. (c) Illustration of m-Torquer-mediated magnetomechanogenetics. (d) Behavior modulation in freely moving animals by m-Torquer and circular magnet array (CMA). (e) Schematic of ferritin-mediated manipulation of TRPV1 and TRPV4. (f) Changes in blood glucose levels with or without radiofrequency (RF) stimulation. (g) Ca^{2+} influx elicited by magnetoferritin. Adapted with permission from: ref 5, copyright 2015 The American Association for the Advancement of Science; ref 42, copyright 2021 Springer Nature; ref 41, copyright 2016 Springer Nature; ref 44, copyright 2016 Springer Nature.

then transmits the signal to the channel pore via a wedge-shaped motif for activation.[36] As for TRPN (also called NompC), its cytosolic part comprises a giant ankyrin repeat domain linked to transmembrane domains via the TRP motif (Figure 5b).[37] The ankyrin repeat domain can function as a force-sensitive gating spring to twist the TRP domain and consequently rotate the pore closure sites, eventually opening the channel. TRPV4 can be activated by cell swelling, with phospholipase A_2 (PLA_2) and arachidonic acid acting as mediators.[38]

4.3. Magnetogenetics via Thermal and Mechanical Routes

As mentioned earlier, magnetic fields can generate localized heat or induce force to activate thermosensitive or mechanosensitive channels. For this purpose, magnetogenetics is divided into magnetothermogenetics and magnetomechanogenetics.

4.3.1. Magnetothermogenetics. In early 2010, Huang and co-workers[39] tested the possibility of using $MnFe_2O_4$ nanoparticles and an alternating magnetic field to generate heat to open TRPV1 and induce a thermal avoidance response in *C. elegans*. Chen et al.[5] then transferred the system to mammals for evaluation. Fe_3O_4 nanoparticles, modified with polyethylene glycol (Figure 6a), were used to activate TRPV1 in the ventral tegmental area, which ultimately enhanced c-Fos expression (Figure 6b). In addition to neuromodulation, the magnetothermal system can also remotely regulate the production of proteins such as insulin. Stanley et al.[40] coated iron oxide nanoparticles with antibodies to His (anti-His) to enable the particles to target modified TRPV1 with a His × 6 epitope tag in the extracellular region. When tumor xenografts expressing modified insulin genes (TRPV1-dependent insulin secretion) were implanted in a mouse, insulin secretion was induced by radiofrequency stimulation at 465 kHz.

In addition to inorganic magnetic nanoparticles, genetically encoded ferritin was also investigated to avoid the inconvenience of incubation or injection of extracellular nanoparticles. Moreover, because of its genetic coding attribute, ferritin can precisely target the desired molecules via direct gene fusion. Stanley et al.[41] fused ferritin with TRPV1 to construct a genetically encoded magnetogenetic system (Figure 6e). Implantation of the system, which expressed TRPV1 ferritin and the Ca^{2+}-dependent insulin transgene into a rodent, stimulated insulin production by radiofrequency and lowered blood glucose levels (Figure 6f). Longitudinal studies confirmed the efficacy of this system over 6 weeks and demonstrated that it has the potential to affect diabetic conditions.

4.3.2. Magnetomechanogenetics. Magnetic nanoparticles can convert magnetic fields into local mechanical force, making it possible to manipulate mechanosensitive ion channels remotely. Recently, a Piezo1-based magnetogenetic tool called "m-Torquer" was developed to modulate the behavior of freely moving rodents (Figure 6c).[42] The m-Torquer (~500 nm in diameter) consists of a spherical support and a monolayer of octahedral iron oxide nanoparticles with an inverse-spinel structure (~25 nm diameter). Using a rotating circular magnet array, the torque force induced by the m-Torquer activated Piezo1 and regulated mouse locomotion (Figure 6d). This system takes full advantage of magnetic fields in tissue penetration and enables neuromodulation in freely moving mice. Additionally, mechanosensitive TRPV4 has also

https://doi.org/10.1021/accountsmr.1c00251
Acc. Mater. Res. 2022, 3, 247−258

been manipulated through the use of magnetic nanoparticles to control animal behaviors.[43]

Ferritin also has the potential to enable magnetomechanical actuation. Wheeler et al.[44] have engineered a genetically encoded actuator "Magneto" containing TRPV4 and a fused ferritin (Figure 6e). When "Magneto" was expressed in mammalian cells, magnetic stimulation of ~50 mT was sufficient to activate TRPV4, triggering a Ca^{2+} influx into cells and controlling the tactile response in zebrafish (Figure 6g). Notably, "Magneto" broadly activated distributed $D1R^{+}$ neurons in the striatum that controls complex reward behavior.

It is noteworthy that the energy conversion efficiency of magnetogenetics needs further improvement, especially for the "magneto" system whose effectiveness is still under debate. Nevertheless, the dual power of magnetothermal and magneto-mechanical conversion makes target molecules abundantly available for magnetogenetics. Furthermore, because magnetic field stimulation has superior tissue penetration compared with illumination, magnetogenetics can stimulate scattered cell populations, making it a complementary tool for optogenetics and photothermogenetics.

5. OTHER MANIPULATION APPROACHES

Apart from light and magnetic fields, other forms of physical signals with significant tissue penetration such as ultrasound have emerged to enrich the toolbox for ion channel manipulation. The acoustic force generated by ultrasound can directly activate mechanosensitive channels with high conductance and Piezo1 to excite neurons (Figure 7a).[45,46]

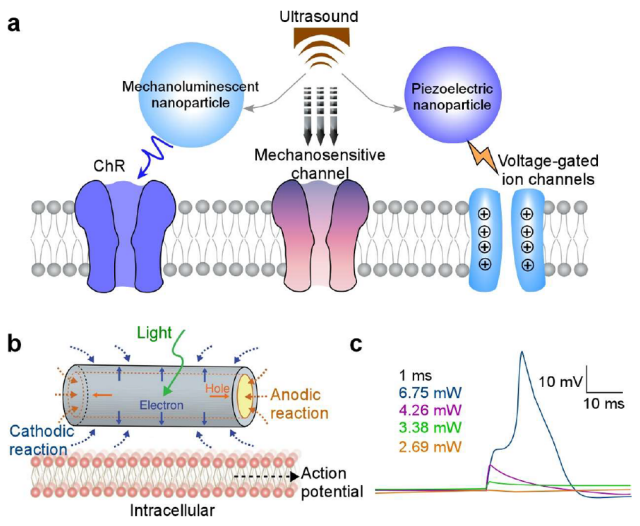

Figure 7. Various approaches for ion channel manipulation. (a) Ultrasonic activation of light-sensitive, mechanosensitive, and voltage-gated ion channels. (b) Coaxial p-type/intrinsic/n-type Si nanowire-mediated generation of photocurrent inducing membrane depolarization. (c) Changes of membrane potential evoked by PIN-SiNW at different laser powers. Adapted with permission from ref 49, copyright 2018 Springer Nature.

However, tiny transmitting and receiving devices are highly desirable to convert ultrasound into a localized force, in part because they are required to localize the signal and avoid cross-contamination. In addition to force, ultrasound can also be converted to blue light using mechanoluminescent nanoparticles, making it possible to activate ChR2 and control neuronal activity.[47] Membrane potential and voltage-gated ion channels (VGICs) are essential factors for modulating neuronal action potentials. Piezoelectric nanomaterials such as tetragonal barium titanate nanoparticles have recently been used to convert ultrasound into an electric field that activates voltage-gated ion channels.[48] In addition, silicon nanowires have been reported to directly modulate membrane potential and control neuronal activity. Coaxial p-type/intrinsic/n-type Si nanowires have been synthesized to convert 532 nm light into current that triggers neuronal action potentials (Figure 7b,c).[49] Although the exploration of sonogenetics and photoelectrochemical systems is relatively preliminary, it would expand the genetic toolbox, especially for situations where illumination has a negligible effect or where voltage-gated channels need to be modulated.

6. CURRENT CHALLENGES AND PERSPECTIVES

Emerging nanotechnologies such as UCNP-based optogenetics, photothermogenetics, and magnetogenetics, have opened new landscapes for rapid, precise, and minimally invasive control of ion channel activities, enabling remote neuromodulation and therapeutics. These tools are also likely to enable modulation of other biological processes, including metabolism, homeostasis, hormone secretion, and gene expression.

Despite the tantalizing prospects, these technologies are still in their infancy and several issues remain to be addressed. First, the biocompatibility and biodegradability of nanoparticles are of concern, and the issue of long-term biosafety requires further investigation prior to clinical translation. The size, morphology, chemical composition, and surface activity of nanoparticles have been shown to be closely related to the toxicity of nanomaterials.[50] Therefore, one way to reduce the persistent toxicity risk is to develop nanoparticles that can be removed or biodegraded after they have completed their tasks. An alternative strategy is to develop genetically encoded protein-based nanoparticles instead of exogenously synthetic nanoparticles. Second, nanoparticle targeting remains a critical factor for precise and efficient manipulation. Currently, the most commonly used method is conjugation with antibodies. However, the development of more effective and practical targeting strategies is highly desirable. Third, the penetration depth of NIR-based techniques is limited to the millimeter range. An alternative optogenetic approach is based on high-energy X-rays that can penetrate the entire body. However, radiation risks must be considered and resolved.[51,52]

In closing, each technique has its own strengths and weaknesses. The integration of different modulation approaches will provide a unique opportunity to address challenges in biological domains and develop translational manipulation tools.

AUTHOR INFORMATION

Corresponding Author

Xiaogang Liu − *Department of Chemistry, National University of Singapore, Singapore 117543, Singapore; The N.1 Institute for Health, National University of Singapore, Singapore 117456, Singapore;* orcid.org/0000-0003-2517-5790; Email: chmlx@nus.edu.sg

Authors

Yuxia Liu − *Department of Chemistry, National University of Singapore, Singapore 117543, Singapore; The N.1 Institute*

https://doi.org/10.1021/accountsmr.1c00251
Acc. Mater. Res. 2022, 3, 247−258

for Health, National University of Singapore, Singapore 117456, Singapore

Zhigao Yi − *Department of Chemistry, National University of Singapore, Singapore 117543, Singapore; The N.1 Institute for Health, National University of Singapore, Singapore 117456, Singapore;* orcid.org/0000-0003-0853-2055

Yun Yao − *Department of Neurobiology, Peking University, Beijing 100191, P.R. China*

Bing Guo − *School of Science, Harbin Institute of Technology (Shenzhen), Shenzhen 518055, P.R. China;* orcid.org/0000-0001-7981-0644

Complete contact information is available at: https://pubs.acs.org/10.1021/accountsmr.1c00251

Notes

The authors declare no competing financial interest.

Biographies

Yuxia Liu received her B.E. degree in Biomedical Engineering from Xi'an Jiaotong University, China. She earned her Ph.D. degree in Biomedical Engineering from Tsinghua University, China. Since 2020, she has been working in Professor Xiaogang Liu's group at the National University of Singapore. Her current research focuses on the development of novel nanotechnologies that enable better understanding of membrane-related biological behaviors, neuronal mechanisms, and therapeutic interventions.

Zhigao Yi earned his B.S. degree in Packaging Materials and Engineering from Hunan University of Science and Technology, China. He received his Master's degree in Materials Science and Engineering from Xiangtan University, China, and completed his Ph.D. studies in Professor Xiaogang Liu's research group at the National University of Singapore in 2019. His current research interest is the design of multifunctional nanomaterials for bioimaging, phototherapy, and neuromodulation.

Yun Yao received her B.E. degree in Biomedical Engineering from Tianjin Medical University in 2015 and completed her Ph.D. study in Biomedical Engineering from Tsinghua University in 2020. She currently works as a technician supervisor at Peking University. Her research interest falls in neurobiological studies of emotional perception, reward and pain perception.

Bing Guo received his B.S. degree in Polymer Materials and Engineering from Zhengzhou University and got his M.S. degree in Polymer Chemistry from The Hong Kong Polytechnic University. He earned his Ph.D. degree and worked as a postdoctoral researcher in Chemical and Biomolecular Engineering at the National University of Singapore for one year. He then moved to Harbin Institute of Technology (Shenzhen) as an associate professor in 2020. His current research focuses on the development of organic materials for molecular imaging, therapy, and photoelectric applications.

Xiaogang Liu received his B.E. degree in chemical engineering from Beijing Technology and Business University, China. He received his M.S. degree in chemistry from East Carolina University and his Ph.D. degree from Northwestern University. He then worked as a postdoctoral researcher at the Massachusetts Institute of Technology for two years before moving to the National University of Singapore in 2006. He is currently an associate editor of Nanoscale and serves on the editorial boards of *Research*, *Nanoscale Horizons*, *Chemistry: An Asian Journal*, *Advanced Optical Materials*, *Analysis and Sensing*, *Journal of Luminescence*, and *The Journal of Physical Chemistry Letters*. His research includes catalysis, molecular sensing, and biomedicine, as well as the development of luminescent nanomaterials for optogenetic neuromodulation, cancer immunotherapy, assistive technologies, and X-ray imaging.

ACKNOWLEDGMENTS

This work was supported by the National Research Foundation, Prime Minister's Office, Singapore, under the NRF Investigatorship Programme (Award No. NRF-NRFI05-2019-0003), NUS NANONASH Programme (NUHSRO/2020/002/NanoNash/LOA; R143000B43114), Initiation Grant Faculty Niche Research Areas Fund (RC-FNRA-IG/20-21/SCI/02), the Science and Technology Innovation Commission of Shenzhen (RCBS20200714114910141, JCYJ20210324132816039), and the Start-up Grant at Harbin Institute of Technology (Shenzhen), China (HA45001108, HA11409049).

REFERENCES

(1) Hille, B. *Ion Channels of Excitable Membranes*; Sinauer: , Sunderland, MA, 2001.

(2) Poth, K. M.; Texakalidis, P.; Boulis, N. M. Chemogenetics: Beyond Lesions and Electrodes. *Neurosurgery* **2021**, *89*, 185−195.

(3) Marshel, J. H.; Kim, Y. S.; Machado, T. A.; Quirin, S.; Benson, B.; Kadmon, J.; Raja, C.; Chibukhchyan, A.; Ramakrishnan, C.; Inoue, M.; Shane, J. C.; McKnight, D. J.; Yoshizawa, S.; Kato, H. E.; Ganguli, S.; Deisseroth, K. Cortical layer-specific critical dynamics triggering perception. *Science* **2019**, *365*, eaaw5202.

(4) 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*, 679−684.

(5) Chen, R.; Romero, G.; Christiansen, M. G.; Mohr, A.; Anikeeva, P. Wireless magnetothermal deep brain stimulation. *Science* **2015**, *347*, 1477−1480.

(6) Zhou, B.; Shi, B. Y.; Jin, D. Y.; Liu, X. G. Controlling upconversion nanocrystals for emerging applications. *Nat. Nanotechnol.* **2015**, *10*, 924−936.

(7) Deisseroth, K.; Hegemann, P. The form and function of channelrhodopsin. *Science* **2017**, *357*, eaan5544.

(8) Fenno, L.; Yizhar, O.; Deisseroth, K. The Development and Application of Optogenetics. *Annu. Rev. Neurosci.* **2011**, *34*, 389−412.

(9) Airan, R. D.; Thompson, K. R.; Fenno, L. E.; Bernstein, H.; Deisseroth, K. Temporally precise in vivo control of intracellular signalling. *Nature* **2009**, *458*, 1025−1029.

(10) Chen, R.; Gore, F.; Nguyen, Q. A.; Ramakrishnan, C.; Patel, S.; Kim, S. H.; Raffiee, M.; Kim, Y. S.; Hsueh, B.; Krook-Magnusson, E.; Soltesz, I.; Deisseroth, K. Deep brain optogenetics without intracranial surgery. *Nat. Biotechnol.* **2021**, *39*, 161−164.

(11) He, L.; Zhang, Y. W.; Ma, G. L.; Tan, P.; Li, Z. J.; Zang, S. B.; Wu, X.; Jing, J.; Fang, S. H.; Zhou, L. J.; Wang, Y. J.; Huang, Y.; Hogan, P. G.; Han, G.; Zhou, Y. B. Near-infrared photoactivatable control of Ca^{2+} signaling and optogenetic immunomodulation. *Elife* **2015**, *4*, e10024.

(12) He, L.; Wang, L. Q.; Zeng, H. X.; Tan, P.; Ma, G. L.; Zheng, S. S.; Li, Y. X.; Sun, L.; Dou, F.; Siwko, S.; Huang, Y.; Wang, Y. J.; Zhou, Y. B. Engineering of a bona fide light-operated calcium channel. *Nat. Commun.* **2021**, *12*, 164.

(13) Yi, Z. G.; Luo, Z. C.; Qin, X.; Chen, Q. S.; Liu, X. G. Lanthanide-Activated Nanoparticles: A Toolbox for Bioimaging, Therapeutics, and Neuromodulation. *Acc. Chem. Res.* **2020**, *53*, 2692−2704.

(14) All, A. H.; Zeng, X.; Teh, D. B. L.; Yi, Z. G.; Prasad, A.; Ishizuka, T.; Thakor, N.; Hiromu, Y.; Liu, X. G. Expanding the Toolbox of Upconversion Nanoparticles for In Vivo Optogenetics and Neuromodulation. *Adv. Mater.* **2019**, *31*, 1803474.

(15) Shah, S.; Liu, J. J.; Pasquale, N.; Lai, J. P.; McGowan, H.; Pang, Z. P.; Lee, K. B. Hybrid upconversion nanomaterials for optogenetic neuronal control. *Nanoscale* **2015**, *7*, 16571−16577.
(16) 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.
(17) Ma, Y. Q.; Bao, J.; Zhang, Y. W.; Li, Z. J.; Zhou, X. Y.; Wan, C. L.; Huang, L.; Zhao, Y.; Han, G.; Xue, T. Mammalian Near-Infrared Image Vision through Injectable and Self-Powered Retinal Nano-antennae. *Cell* **2019**, *177*, 243−255.
(18) Mei, Q. S.; Bansal, A.; Jayakumar, M. K. G.; Zhang, Z. M.; Zhang, J.; Huang, H.; Yu, D. J.; 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.
(19) Liu, X.; Chen, H.; Wang, Y.; Si, Y.; Zhang, H.; Li, X.; Zhang, Z.; Yan, B.; Jiang, S.; Wang, F.; Weng, S.; Xu, W.; Zhao, D.; Zhang, J.; Zhang, F. Near-infrared manipulation of multiple neuronal populations via trichromatic upconversion. *Nat. Commun.* **2021**, *12*, 5662.
(20) Zeng, X.; Chen, S.; Weitemier, A.; Han, S. Y.; Blasiak, A.; Prasad, A.; Zheng, K. Z.; Yi, Z. G.; Luo, B. W.; Yang, I. H.; Thakor, N.; Chai, C.; Lim, K. L.; McHugh, T. J.; All, A. H.; Liu, X. G. Visualization of Intra-neuronal Motor Protein Transport through Upconversion Microscopy. *Angew. Chem., Int. Ed.* **2019**, *58*, 9262−9268.
(21) Yi, Z. G.; Gao, H. X.; Ji, X. L.; Yeo, X. Y.; Chong, S. Y.; Mao, Y. J.; Luo, B. W.; Shen, C.; Han, S. Y.; Wang, J. W.; Jung, S. Y.; Shi, P.; Ren, H. L.; Liu, X. G. Mapping Drug-Induced Neuropathy through In-Situ Motor Protein Tracking and Machine Learning. *J. Am. Chem. Soc.* **2021**, *143*, 14907−14915.
(22) Venkatachalam, K.; Montell, C. TRP channels. *Annu. Rev. Biochem.* **2007**, *76*, 387−417.
(23) Hilton, J. K.; Kim, M.; Van Horn, W. D. Structural and Evolutionary Insights Point to Allosteric Regulation of TRP Ion Channels. *Acc. Chem. Res.* **2019**, *52*, 1643−1652.
(24) Li, Y. B.; Lu, W.; Huang, Q. A.; Huang, M. A.; Li, C.; Chen, W. Copper sulfide nanoparticles for photothermal ablation of tumor cells. *Nanomedicine* **2010**, *5*, 1161−1171.
(25) Li, J. C.; Pu, K. Y. Semiconducting Polymer Nanomaterials as Near-Infrared Photoactivatable Protherapeutics for Cancer. *Acc. Chem. Res.* **2020**, *53*, 752−762.
(26) Nakatsuji, H.; Numata, T.; Morone, N.; Kaneko, S.; Mori, Y.; Imahori, H.; Murakami, T. Thermosensitive Ion Channel Activation in Single Neuronal Cells by Using Surface-Engineered Plasmonic Nanoparticles. *Angew. Chem., Int. Ed.* **2015**, *54*, 11725−11729.
(27) Li, B. H.; Yin, Y. W.; Liu, Y.; Pi, Y.; Guo, L.; Cao, X. J.; Gao, C. Y.; Zhang, L. L.; Li, J. C. TRPV1 activation impedes foam cell formation by inducing autophagy in oxLDL-treated vascular smooth muscle cells. *Cell. Death. Dis.* **2014**, *5*, e1182.
(28) Gao, W.; Sun, Y. H.; Cai, M.; Zhao, Y. J.; Cao, W. H.; Liu, Z. H.; Cui, G. W.; Tang, B. Copper sulfide nanoparticles as a photothermal switch for TRPV1 signaling to attenuate atherosclerosis. *Nat. Commun.* **2018**, *9*, 231.
(29) Ma, Z. Y.; Zhang, J.; Zhang, W. Y.; Foda, M. F.; Zhang, Y. F.; Ge, L.; Han, H. Y. Intracellular Ca^{2+} Cascade Guided by NIR-II Photothermal Switch for Specific Tumor Therapy. *Iscience* **2020**, *23*, 101049.
(30) Zhang, M.; Song, R. X.; Liu, Y. Y.; Yi, Z. G.; Meng, X. F.; Zhang, J. W.; Tang, Z. M.; Yao, Z. W.; Liu, Y.; Liu, X. G.; Bu, W. B. Calcium-Overload-Mediated Tumor Therapy by Calcium Peroxide Nanoparticles. *Chem.* **2019**, *5*, 2171−2182.
(31) Yu, Y.; Yang, X.; Reghu, S.; Kaul, S. C.; Wadhwa, R.; Miyako, E. Photothermogenetic inhibition of cancer stemness by near-infrared-light-activatable nanocomplexes. *Nat. Commun.* **2020**, *11*, 4117.
(32) Nelidova, D.; Morikawa, R. K.; Cowan, C. S.; Raics, Z.; Goldblum, D.; Scholl, H. P. N.; Szikra, T.; Szabo, A.; Hillier, D.; Roska, B. Restoring light sensitivity using tunable near-infrared sensors. *Science* **2020**, *368*, 1108−1113.
(33) Zhen, X.; Xie, C.; Jiang, Y. Y.; Ai, X. Z.; Xing, B. G.; Pu, K. Y. Semiconducting Photothermal Nanoagonist for Remote-Controlled Specific Cancer Therapy. *Nano Lett.* **2018**, *18*, 1498−1505.
(34) Dobson, J. Remote control of cellular behaviour with magnetic nanoparticles. *Nat. Nanotechnol.* **2008**, *3*, 139−143.
(35) Arosio, P.; Ingrassia, R.; Cavadini, P. Ferritins: A family of molecules for iron storage, antioxidation and more. *BBA-Gen. Subjects.* **2009**, *1790*, 589−599.
(36) Cox, C. D.; Bavi, N.; Martinac, B. Bacterial Mechanosensors. *Annu. Rev. Physiol.* **2018**, *80*, 71−93.
(37) Jin, P.; Bulkley, D.; Guo, Y. M.; Zhang, W.; Guo, Z. H.; Huynh, W.; Wu, S. P.; Meltzer, S.; Cheng, T.; Jan, L. Y.; Jan, Y. N.; Cheng, Y. F. Electron cryo-microscopy structure of the mechanotransduction channel NOMPC. *Nature* **2017**, *547*, 118−122.
(38) Ryskamp, D. A.; Jo, A. O.; Frye, A. M.; Vazquez-Chona, F.; MacAulay, N.; Thoreson, W. B.; Krizaj, D. Swelling and Eicosanoid Metabolites Differentially Gate TRPV4 Channels in Retinal Neurons and Glia. *J. Neurosci.* **2014**, *34*, 15689−15700.
(39) Huang, H.; Delikanli, S.; Zeng, H.; Ferkey, D. M.; Pralle, A. Remote control of ion channels and neurons through magnetic-field heating of nanoparticles. *Nat. Nanotechnol.* **2010**, *5*, 602−606.
(40) Stanley, S. A.; Gagner, J. E.; Damanpour, S.; Yoshida, M.; Dordick, J. S.; Friedman, J. M. Radio-Wave Heating of Iron Oxide Nanoparticles Can Regulate Plasma Glucose in Mice. *Science* **2012**, *336*, 604−608.
(41) Stanley, S. A.; Kelly, L.; Latcha, K. N.; Schmidt, S. F.; Yu, X. F.; Nectow, A. R.; Sauer, J.; Dyke, J. P.; Dordick, J. S.; Friedman, J. M. Bidirectional electromagnetic control of the hypothalamus regulates feeding and metabolism. *Nature* **2016**, *531*, 647−650.
(42) Lee, J. U.; Shin, W.; Lim, Y.; Kim, J.; Kim, W. R.; Kim, H.; Lee, J. H.; Cheon, J. Non-contact long-range magnetic stimulation of mechanosensitive ion channels in freely moving animals. *Nat. Mater.* **2021**, *20*, 1029−1036.
(43) Wu, S. F.; Li, H.; Wang, D. Q.; Zhao, L. M.; Qiao, X.; Zhang, X.; Liu, W.; Wang, C. Y.; Zhou, J. Genetically magnetic control of neural system via TRPV4 activation with magnetic nanoparticles. *Nano Today* **2021**, *39*, 101187.
(44) Wheeler, M. A.; Smith, C. J.; Ottolini, M.; Barker, B. S.; Purohit, A. M.; Grippo, R. M.; Gaykema, R. P.; Spano, A. J.; Beenhakker, M. P.; Kucenas, S.; Patel, M. K.; Deppmann, C. D.; Guler, A. D. Genetically targeted magnetic control of the nervous system. *Nat. Neurosci.* **2016**, *19*, 756−761.
(45) Ye, J.; Tang, S. Y.; Meng, L.; Li, X.; Wen, X. X.; Chen, S. H.; Niu, L. L.; Li, X. Y.; Qiu, W. B.; Hu, H. L.; Jiang, M. Z.; Shang, S. Q.; Shu, Q.; Zheng, H. R.; Duan, S. M.; Li, Y. Z. Ultrasonic Control of Neural Activity through Activation of the Mechanosensitive Channel MscL. *Nano Lett.* **2018**, *18*, 4148−4155.
(46) Qiu, Z. H.; Guo, J. H.; Kala, S.; Zhu, J. J.; Xian, Q. X.; Qiu, W. B.; Li, G. F.; Zhu, T.; Meng, L.; Zhang, R.; Chan, H. C.; Zheng, H. R.; Sun, L. The Mechanosensitive Ion Channel Piezo1 Significantly Mediates In Vitro Ultrasonic Stimulation of Neurons. *Iscience* **2019**, *21*, 448−457.
(47) Wu, X.; Zhu, X. J.; Chong, P.; Liu, J. L.; Andre, L. N.; Ong, K. S.; Brinson, K.; Mahdi, A. I.; Li, J. C.; Fenno, L. E.; Wang, H. L.; Hong, G. S. Sono-optogenetics facilitated by a circulation- delivered rechargeable light source for minimally invasive optogenetics. *Proc. Natl. Acad. Sci. U.S.A.* **2019**, *116*, 26332−26342.
(48) Marino, A.; Arai, S.; Hou, Y. Y.; Sinibaldi, E.; Pellegrino, M.; Chang, Y. T.; Mazzolai, B.; Mattoli, V.; Suzuki, M.; Ciofani, G. Piezoelectric Nanoparticle-Assisted Wireless Neuronal Stimulation. *ACS Nano* **2015**, *9*, 7678−7689.
(49) Parameswaran, R.; Carvalho-de-Souza, J. L.; Jiang, Y. W.; Burke, M. J.; Zimmerman, J. F.; Koehler, K.; Phillips, A. W.; Yi, J.; Adams, E. J.; Bezanilla, F.; Tian, B. Z. Photoelectrochemical modulation of neuronal activity with free-standing coaxial silicon nanowires. *Nat. Nanotechnol.* **2018**, *13*, 260−266.

https://doi.org/10.1021/accountsmr.1c00251
Acc. Mater. Res. 2022, 3, 247−258

(50) Jiang, W.; Kim, B. Y. S.; Rutka, J. T.; Chan, W. C. W. Nanoparticle-mediated cellular response is size-dependent. *Nat. Nanotechnol.* **2008**, *3*, 145−150.
(51) Chen, Z. W.; Tsytsarev, V.; Finfrock, Y. Z.; Antipova, O. A.; Cai, Z. H.; Arakawa, H.; Lischka, F. W.; Hooks, B. M.; Wilton, R.; Wang, D. Y.; Liu, Y.; Gaitan, B.; Tao, Y.; Chen, Y.; Erzurumlu, R. S.; Yang, H. H.; Rozhkova, E. A. Wireless Optogenetic Modulation of Cortical Neurons Enabled by Radioluminescent Nanoparticles. *ACS Nano* **2021**, *15*, 5201−5208.
(52) Matsubara, T.; Yanagida, T.; Kawaguchi, N.; Nakano, T.; Yoshimoto, J.; Sezaki, M.; Takizawa, H.; Tsunoda, S. P.; Horigane, S.-i.; Ueda, S.; Takemoto-Kimura, S.; Kandori, H.; Yamanaka, A.; Yamashita, T. Remote control of neural function by X-ray-induced scintillation. *Nat. Commun.* **2021**, *12*, 4478.

https://doi.org/10.1021/accountsmr.1c00251
Acc. Mater. Res. 2022, 3, 247−258