Smart Materials Meet Multifunctional Biomedical Devices: Current and Prospective Implications for Nanomedicine

Giada Graziana Genchi1*, Attilio Marino1, Christos Tapeinos1 and Gianni Ciofani1,2*

1 Smart Bio-Interfaces, Istituto Italiano di Tecnologia, Pontedera, Italy, 2 Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Torino, Italy

With the increasing advances in the fabrication and in monitoring approaches of nanotechnology devices, novel materials are being synthesized and tested for the interaction with biological environments. Among them, smart materials in particular provide versatile and dynamically tunable platforms for the investigation and manipulation of several biological activities with very low invasiveness in hardly accessible anatomical districts. In the following, we will briefly recall recent examples of nanotechnology-based materials that can be remotely activated and controlled through different sources of energy, such as electromagnetic fields or ultrasounds, for their relevance to both basic science investigations and translational nanomedicine. Moreover, we will introduce some examples of hybrid materials showing mutually beneficial components for the development of multifunctional devices, able to simultaneously perform duties like imaging, tissue targeting, drug delivery, and redox state control. Finally, we will highlight challenging perspectives for the development of theranostic agents (merging diagnostic and therapeutic functionalities), underlining open questions for these smart nanotechnology-based devices to be made readily available to the patients in need.

Keywords: smart materials, remote stimulation, drug delivery, immune system, tissue engineering

INTRODUCTION

Smart materials have gained increasing attention in the biomedical research fields thanks to their adjustable physical and/or chemical properties in response to deliberately imparted external stimuli or to environmental changes. For these reasons, their introduction in nanomedicine has opened unprecedented possibilities of manipulation of biological entities at cellular and even sub-cellular level. In this scenario, the intrinsic properties of nanoparticles or nanotextured materials are exploited, providing active devices capable of diagnostic, therapeutic or even theranostic functions. When physical cues like light irradiation, ultrasounds, or electromagnetic fields are applied to a smart nanostructure, an energy transduction occurs and results into the activation of a precise cellular functionality. Moreover, a suitable modification of the nanoparticle surface (e.g., with the aid of a cell ligand or of a monoclonal antibody) can improve the efficacy of this activation, by targeting specific cell populations or even specific intracellular organelles. This approach, which can be defined as a new paradigm in nanomedicine, finds several applications including cancer therapy, drug delivery, tissue engineering, and even bionics.
In this mini-review, we will focus on those nanomaterials that, in our opinion, are the most promising in terms of clinical translation, with particular attention to nanoparticles that act as “nano-transducers,” allowing for a remote manipulation of biological activities, and thus providing a “smart” interface between biological and non-biological environments (Figure 1).

REMOTE CELL STIMULATION THROUGH SMART NANOMATERIALS

The possibility to finely and remotely manipulate cell behavior in deep tissues is of extreme importance in medicine for restoring physiological cell activities after the onset of a pathological condition (Dell’Anno et al., 2014; Li et al., 2017). Furthermore, the remote control of cell activities in vivo allows the elucidation of mechanisms at the base of different diseases and the development of novel therapeutic strategies (Brunoni et al., 2012; Paz et al., 2013; Legon et al., 2014).

A consolidated method for the fine modulation of the activity of specific cell types is represented by optogenetics, which consists in the genetic sensitization of targeted cells to light through a promoter-driven expression of light-sensitive proteins. Alternatively, a new generation of smart nanomaterial-based approaches for the remote control of cell behavior has recently been proposed (Genchi et al., 2017a). Smart nanomaterials can be externally/wirelessly activated by different energy sources [e.g., near-infrared (NIR) radiations, radiofrequency stimulations, magnetic fields, ultrasounds, etc.] that are able to penetrate biological tissues efficiently and non-invasively. Nanostructure activation in deep tissues triggers specific behaviors (e.g., neural spikes and myocyte contractions) (Eom et al., 2014; Colombo et al., 2016; Marino et al., 2017a), or tunes biochemical pathways involved in different cell activities, such as differentiation (Kim et al., 2016; Rau et al., 2016), morphological maturation (Ciofani et al., 2010), and hormone release (Stanley et al., 2012, 2015). These energy-driven nanoparticle-mediated approaches are able to overcome the scarce tissue penetration by visible light and the use of viruses to genetically modify target cells, which are the main drawbacks currently limiting clinical applications of optogenetics (Jarvis and Schultz, 2015).

Piezoelectric nanomaterials are a class of nanostructures able to generate a voltage on their surface when exposed to a mechanical stimulation, for example by means of ultrasounds, US (Wang et al., 2007). This voltage has been used for the stimulation of electrically excitable cells, like neurons (Ciofani et al., 2010; Royo-Gascon et al., 2013; Hoop et al., 2017; Lee et al., 2017) and bone cells (Genchi et al., 2017b). Our group demonstrated for the first time that the acute US-driven piezo-stimulation of barium titanate nanoparticles (BTNPs) associated to plasma membrane was able to significantly increase the intracellular calcium concentration in neural cells (Marino et al., 2015). The combination of US and non-piezoelectric BTNPs was not able to elicit a significant neural response, thus confirming that the mechanism was mediated by piezoelectricity and not by other unspecified phenomena (e.g., mechanical or thermal).

**FIGURE 1** | Schematic representation of various multifunctional nanostructures, their responsive stimuli, and their main biomedical applications.
Another wide-spread approach for remote cell activation is represented by nanoparticle-assisted heat stimulation by short-duration temperature increments in a physiological range (of about 5°C) (Shapiro et al., 2012). A local increment of temperature can be obtained by exploiting different energy transduction approaches, such as the photothermal and the magnetothermal ones. Photothermal stimulation consists in the transduction of photon energy into heat and can be remotely triggered with NIR radiation in combination with many plasmonic nanomaterials, such as gold nanoshells (Erickson and Tunnell, 2010), gold nanorods (Huang et al., 2006), single-walled carbon nanotubes (Mocan et al., 2011), graphene oxide (Robinson et al., 2011), and copper sulfide (Cu2S) nanocrystals (Wang et al., 2015). Different independent works showed that photothermal stimulation is able to reversibly elicit a neural response in terms of spike activity, intracellular calcium levels, and neurite outgrowth (Yong et al., 2014; Paviolo and Stoddart, 2017). These effects seem to be mediated by the opening of temperature-sensitive calcium channels (Miyako et al., 2014) and/or by heat-dependent capacitance changes of the neural plasma membrane (Carvalho-de-Souza et al., 2015).

However, the mechanisms of photothermal stimulation on complex neural networks have to be further investigated. Indeed, a recent work documented an inhibited neural network activity of hippocampal primary culture treated with gold nanorods upon NIR irradiation (Yoo et al., 2014). Remote photothermal nerve activation was successfully used for inducing leg muscle contraction in frogs after treatment with carbon nanohorns and NIR irradiation (Miyako et al., 2014). Similarly to neural cells, muscle cells can be stimulated by heat: in this concern, our group has recently demonstrated that an acute NIR irradiation of gold nanoshell-containing cultures is able to induce myotube contraction, while a chronic one suggested to promote mitochondrial genesis (Marino et al., 2017a).

Alternatively to photothermal stimulation, magnetothermal transduction can be exploited for cell heating/stimulation. In this case, magnetic nanoparticles dissipate heat when undergo an alternate electric field (Noh et al., 2017). In a recent work, this approach was exploited for remote deep stimulation of the ventral tegmental area (VTA) through the opening of a transfected heat-sensitive receptor TRPV1 in mice. The consequent increase of neural activity was also observed in the brain areas receiving excitatory projections from VTA. Interestingly, the retention period of the magnetic nanoparticles in the VTA was longer than a month, thus allowing for chronic magnetothermal VTA stimulations (Chen et al., 2015).

Other nanomaterial-assisted remote stimulation methods exploit magnetoellectric and optoelectric phenomena (Colombo et al., 2016; Wang and Guo, 2016). Concerning magnetoellectric materials, cobalt ferrite–barium titanate (CoFe2O4–BaTiO3) core-shell nanoparticles were used to modulate deep-brain activity under a low-intensity alternating magnetic field (Guduru et al., 2015). Moreover, the magnetic properties of these nanoparticles also facilitated their delivery to the central nervous system (CNS). Indeed, CoFe2O4–BaTiO3 nanoparticles were intravenously administered in mouse tail and forced to cross the blood-brain barrier (BBB) with a static magnetic field.

Regarding the frontiers of optoelectronic bio-interfaces, polymeric biocompatible organic nanoparticles/films of poly(3-hexylthiophene) revealed great performances both in restoring the functionality of blind retinas on ex vivo models [i.e., explants of rat retinas characterized by photoreceptor degeneration (Ghezzi et al., 2013)], and in modulating the behavior of eyeless animals (i.e., freshwater polyps) by amplifying the function of their primitive photoreceptors (Tortiglione et al., 2017).

As a further example, a class of nanomaterials characterized by elements with high atomic number Z (e.g., Au/Pt nanoparticles) can be also exploited as contrast agents and sensitizers of X-rays, representing very promising nanovectors for cancer theranostics (Subiel et al., 2016). The great versatility and potential of these nanomaterials in nanomedicine is noteworthy, especially considering their great potential also in proton therapy (Schlatholter et al., 2016).

**MULTIFUNCTIONAL DRUG DELIVERY SYSTEMS (MDDS)**

The optimization of carriers for delivering drugs specifically to diseased areas originated from the need to overcome drug limitations, such as cytotoxicity, immunogenicity, short circulation times, non-controlled bio-distribution, and the non-targeting ability toward specific tissues. During recent years, significant advancements in the field of nanobiotechnology led to the development of MDDS for the accomplishment of diagnostic and therapeutic purposes through a single medical device, able of performing bio-imaging duties, while improving the therapeutic efficacy of drugs available on the market. MDDS already presented in the literature can have a variety of morphologies and sizes, and can be made of various materials like natural and synthetic polymers, lipids, and other inorganic and organic materials. Nanostructures made of polymeric materials are the most used MDDS, due to a number of advantages, including the high versatility during their fabrication, their controllable size and shape, their high encapsulation efficiency, and their easy surface functionalization by numerous targeting groups, including peptides, proteins, and antibodies. Furthermore, coating of these nanostructures with stealth materials like poly(ethylene glycol), PEG, increases their circulation time inside the body. In combination with the targeting ability, this renders them suitable for the specific delivery of a number of therapeutic preparations, including drugs, enzymes, proteins, RNA, and DNA (Mura et al., 2013; Srinivasan et al., 2015; Bose et al., 2016; Lu et al., 2016) to specific diseased tissues. The most used polymeric nanostructures are nanoparticles, nanocapsules, dendrimers, nanospheres, spherical and worm-like micelles, nanotubes, and hydrogels (Theato et al., 2013; Torchilin, 2014; Lu et al., 2016).

Another category of nanomaterials used as MDDS is represented by lipid nanostructures, including niosomes, transfersomes, liposomes, solid lipid nanoparticles, and nanostructured lipid carriers. Lipid-based nanostructures are considered a better alternative compared to polymeric nanostructures, especially for the treatment of CNS diseases, due to their inherent biocompatibility,
low immunogenicity, and their ability to penetrate the BBB. A newer approach, similar to that of lipid-based nanostructures, but more biomimetic, relies on cell membrane-derived vesicles or the coating of existing nanoparticles such as poly(lactide-co-glycolide) and magnetite nanoparticles with the cell membrane of various cells, like macrophages, neutrophils, red blood cells, cancer cells, and others (Fang et al., 2014; Luk and Zhang, 2015; Bose et al., 2016; Gao et al., 2016; Krishnamurthy et al., 2016).

Inorganic nano- and microparticles, including magnetite (Fe3O4), maghemite (γ-Fe2O3), manganese dioxide (MnO2), cerium dioxide (CeO2), platinum (Pt), silver (Ag), zinc oxide (ZnO), silica (SiO2), titanium dioxide (TiO2), and others, have also been used as MDDS combining various functionalities, such as imaging and hyperthermia (Hayashi et al., 2013; Tapeinos et al., 2016), reactive oxygen species (ROS) scavenging and oxygen generation (Bizeau et al., 2017; Tapeinos et al., 2017), and antimicrobial and anticancer activities (Mohanta et al., 2017).

A combination of the above-mentioned structures like polymers and lipids, polymers and inorganic nanoparticles, and lipids and inorganic nanoparticles have also been studied aiming at further improving the multifunctionality and the therapeutic effect of these nanostructures. Our group, for instance, used a lipid matrix to encapsulate iron oxide nanoparticles and the drug sorafenib, and subsequently showed its magnetically-driven accumulation in vitro against hepatocarcinoma cells, demonstrating localized therapy (Grillone et al., 2015). A combination of inorganic and polymeric nanoparticles have also been used for multimodal imaging of breast cancer tissue (Cheng et al., 2012), providing a more precise imaging through luminescence and magnetic resonance.

The multifunctionality of each one of the above-mentioned nanostructures derives from the combination of materials with specific characteristics and can be translated as the response of the MDDS to a physical/external and/or a biological/internal stimulus, by changing their morphological (size, shape) and/or their physicochemical characteristics (colloidal stability, crystal structure, hydrophobicity, redox state, etc.). To date, numerous systems that respond to external and/or internal stimuli have been developed, but the most important are those ones that respond to more than one stimulus and show ability of a most precise control in the release of the encapsulated therapeutic molecules. Stimuli–responsive systems are usually a combination of polymeric nanostructures and inorganic nanoparticles (Tapeinos et al., 2013, 2016, 2017), although lipid-based nanostructures have also been developed to alter their properties when an external stimulus is applied (Du et al., 2015).

Stimuli-responsive nanostructures that have been used for the treatment of various diseases can respond to physical stimuli, including ultrasounds, light, electric fields, and magnetic fields (Mura et al., 2013; Marino et al., 2015, 2017b,c; Genchi et al., 2016, 2017b), or they can take advantage of the changes in the biological microenvironment of each disease and respond to alterations in temperature, pH, redox conditions, ROS, and enzyme concentration (Tapeinos et al., 2008, 2017; de la Rica et al., 2012; Torchilin, 2014; Tapeinos and Pandit, 2016; Bizeau et al., 2017). Furthermore, a combination of these stimuli (Mura et al., 2013; Tapeinos et al., 2013, 2016; Efthimiadou et al., 2014a,b; Lu et al., 2016) have also been used to increase the therapeutic versatility of the MDDS.

APPLICATIONS AND FUTURE PERSPECTIVES

An increasing number of nanotechnology-based strategies are available for wireless and low-invasiveness manipulation of biological activities in hardly accessible anatomical districts, as the CNS. Among them, ultrasound activation of piezoelectric materials is highly promising for the treatment of deep tissues (Tufail et al., 2011). Further investigations are, however, necessary for selective delivery of piezoelectric nanomaterials to target tissues and retention on site in vivo. The first studies on toxicity and accumulation of piezoelectric boron nitride nanotubes was conducted by our group with rabbits. Our studies collectively demonstrated high biocompatibility in terms of liver, kidney, and blood parameters of high doses (up to 10 mg/kg) of intravenously injected nanotubes (Ciofani et al., 2012, 2013a).

Our group also provided the first evidences on the applicability of piezoelectric nanocomposite films based on poly(vinylidenefluoride-co-trifluoroethylene), P(VDF-TrFE), and BTNPs to neuron-like cell stimulation for cochlear prosthetics. Aiming at compensating missing/altered hair cell function, our nanocomposite films were satisfactorily tested for stimulation of a human neuronal model by direct piezoelectric effect (Genchi et al., 2016). A single US application to films supporting SH-SY5Y cell cultures triggered significantly higher calcium influxes than plain P(VDF-TrFE) films and non-piezoelectric control substrates. Repeated stimulations significantly increased expression of β3-tubulin and neurite extension due to the better piezoelectric properties of composite films, suggesting improved functional maturation of the neuronal model on our artificial cochlear epithelium.

Smart nanomaterials are providing concrete opportunities for the treatment of pathological conditions that affect deep anatomical districts. However, hybrid smart material devices are opening even unprecedented therapeutic opportunities in nanomedicine, like biological barrier overcoming while multiple functions are accomplished (imaging, drug release, etc.). In particular, low-intensity magnetic field stimulation of magnetoelectric nanomaterials holds promise of clinical practice application in the near future. For instance, CoFe2O4–BaTiO3 were validated for Parkinson’s disease treatment in silico (Yue et al., 2012). Moreover, they were successfully tested for magnetically driven BBB crossing, as well as for coupling with and mapping the intrinsic neural activity in mice (Guduru et al., 2015). CoFe2O4–BaTiO3 nanoparticles were also used for direct current-field cell targeting and alternating current-field releasing of anti-HIV drug in vitro (Nair et al., 2013) and of paclitaxel for ovarian cancer treatment in vivo (Rodzinski et al., 2016).

Highly encouraging to the treatment of deep tissues are also cerium dioxide nanomaterials, alone and in combinations with other materials for the control of redox environments (both intercellular and intracellular ones). Our group demonstrated
| Responsive material                  | Stimulus                  | Effect                                                                 | Reference                  |
|-------------------------------------|---------------------------|------------------------------------------------------------------------|----------------------------|
| Au nanorods                          | Photothermal (NIR radiation) | Neuronal spikes                                                        | Eom et al. (2014)          |
| Au@SiO2 nanoshells                  | Photothermal (NIR radiation) | Myotube contractions                                                   | Marino et al. (2017a)      |
| Peptide ligands assembled on carbon nanotubes | Light                     | Cell differentiation                                                   | Kim et al. (2016)          |
| Au nanoparticles                     | Photothermal               | Cell differentiation                                                   | Rau et al. (2016)          |
| Co3S nanocrystals                   | Photothermal and photodynamic (NIR radiation) | Hyperthermia and ROS-induced apoptosis                                | Wang et al. (2015)         |
| Au nanorods                          | Photothermal (NIR radiation) | Cancer cell imaging and photothermal therapy                           | Huang et al. (2006)        |
| Au nanorods                          | Photothermal (NIR radiation) | Inhibition of spontaneous and epileptiform neural activity             | Yoo et al. (2014)          |
| Au nanorods                          | Photothermal (NIR radiation) | Evoking spikes on primary auditory neurons                              | Yong et al. (2014)         |
| Carbon nanohorns                     | Photothermal (NIR radiation) | Nerve activation (opening of the temperature-sensitive calcium channels) | Miyako et al. (2014)       |
| Ultrasmall reduced graphene oxide   | NIR radiation              | Photoablation of U87MG cancer cells                                     | Robinson et al. (2011)     |
| ZnO nanowires                        | Ultrasounds                | Continuous direct-current output                                        | Wang et al. (2007)         |
| BNNTs                                | Ultrasounds                | Neural stimulation (neurite outgrowth)                                  | Ciofani et al. (2010)      |
| BaTiO3 nanoparticles with tetragonal crystal | Ultrasounds                | Neural stimulation (calcium and sodium waves)                          | Marino et al. (2015)       |
| PVDF film                            | Mechanical vibration       | Neural stimulation                                                       | Royo-Gasco et al. (2013)   |
| PVDF membranes                       | Ultrasounds                | Neural differentiation                                                  | Hoop et al. (2017)         |
| P(VDF-TrFe) conduits                 | N/A                        | Regeneration of transected adult rat spinal cord                        | Lee et al. (2017)          |
| P(VDF-TrFe)/BNT composite films      | Ultrasounds                | 1. Stimulation of a human neuronal model                                | Genchi et al. (2016)       |
| High-Z nanomaterials                 | Ultrasounds                | 2. Increased calcium influx                                             |                           |
| Fe3O4 magnetic nanoparticles         | Magnetic field             | 3. Increased expression of β3-tubulin                                   |                           |
| CeO2                                | ROS concentration          | 4. Neurite extension                                                    |                           |
| CoFe2O4–BaTiO3                       | Ultrasounds/static magnetic field | Magnetically guided targeting                                           | Yue et al. (2012)          |
|                                     | Direct current-field       | Cell targeting                                                          | Nair et al. (2013); Rodzinski et al. (2016) |
|                                     | Alternating current-field | Drug release                                                            |                           |
| Fe3O4, γ-Fe2O3                      | Alternating magnetic field | 1. Magnetic resonance imaging                                           | Hayashi et al. (2013); Tapeinos et al. (2016) |
|                                     |                            | 2. Controlled release                                                    |                           |
|                                     |                            | 3. Tumor reduction                                                       |                           |
| MnO2                                | ROS concentration          | ROS scavenging and oxygen generation                                    | Bizeau et al. (2017); Tapeinos et al. (2017) |
| CoFe2O4–BaTiO3                       | Low-intensity alternating magnetic field/static magnetic field | Modulation of deep-brain activity/guided brain targeting                 | Guduru et al. (2015)       |
| Poly(3-hexylthiophene)               | Light                     | Restoration of the functionality of blind retinas                       | Ghezzi et al. (2013)       |
| β-cyclodextrin/Co3O2                 | ROS concentration          | Modulation of the behavior of eyeless animals                           | Tortiglione et al. (2017)  |
| Ferrocene/SiO2                       | Magnetic field NIR irradiation | Intracellular compartment targeting, enhanced antitumoral activity and drug delivery | Xu et al. (2013)           |
| Poly [acrylic acid], Fe3O4, Au, NaYF4, Yb, Er | Static magnetic field | 1. Magnetic resonance imaging                                           | Cheng et al. (2012)        |
| Cetyl palmitate/Fe3O4                | Static magnetic field      | 2. Magnetically targeted photothermal therapy                           | Grillone et al. (2015)     |
| DPPC, DSPE-PEG2000-folate, C60-Fe3O4-PEG2000 | Radiofrequency           | 3. Controlled release                                                    | Du et al. (2015)           |
| DMAEMA, AA, Disulfide, Fe3O4         | Alternating magnetic field | 1. Magnetic resonance imaging                                           | Tapeinos et al. (2013, 2016) |
|                                      | Temperature pH             | 2. Photothermal ablation                                                |                           |
|                                      | GSH concentration          | 3. Controlled release                                                    |                           |
| Carbon-based                         | NIR irradiation            | Stem-cell differentiation                                               | Kim et al. (2016)          |
| Cell membrane of various cells, like macrophages, neutrophils, red blood cells, cancer cells | Laser Irradiation        | Photothermal ablation                                                   | Mocan et al. (2011)        |
| Iron oxide nanoparticles and genetically encoded ferritine nanoparticles | Radiowave heating   | 1. Tumor-specific immune response                                       | Fang et al. (2014); Luk and Zhang (2015); Bose et al. (2016); Gao et al. (2016); Krishnamurthy et al. (2016) |
|                                     |                            | 2. Specific targeting                                                   |                           |
|                                     |                            | 3. Drug delivery                                                        |                           |
|                                     |                            | Enhanced release of encapsulated anticancer drugs                       |                           |
(Continued)
Au nanoparticles Photothermal (light at 532 nm) Evoking spikes to hippocampal neurons through heat-dependent changes of capacitance of the neural plasma membrane Carvalho-de-Souza et al. (2015)

A detailed list of multifunctional nanostructures, their responsive stimuli, and their biological effects can be found in Table 1.

**CONCLUSION**

To date, numerous studies have reported the enhanced therapeutical effect of several nanostructured devices compared to traditional systems. However, a lot of work is still mandatory for these materials to provide a solution to unmet clinical needs. Non-invasive approaches for remote targeting and activation are nowadays available, yet the development of complex and reliable models of biological barriers *in vitro* and *in vivo* is necessary to ensure proper device testing. In our opinion, the enhancement of the capability of intracellular compartment targeting by fine tuning/control of the surface physicochemical properties represents a key step for these smart materials to be made available to the next future clinical practice.

**AUTHOR CONTRIBUTIONS**

GC wrote the Section “Introduction,” GG wrote the Sections “Applications and Future Perspectives” and “Conclusion,” AM wrote the “Remote cell stimulation through smart nanoparticles” Section, and CT wrote the “Multifunctional drug delivery systems” Section and prepared Figure and Table. GC revised the whole manuscript.

**FUNDING**

The preparation of this manuscript was partially supported by the Italian Ministry of Health Grant Number RF-2011-02350464, by the Agenzia Spaziale Italiana Contract Number 2016-7-U.0 (NANOROS), by the European Research Council Grant Number 709613 (SLaMM), by the Compagnia di San Paolo Starting Grant Number 55_A116GC01, and by Fondazione Umberto Veronesi.

**REFERENCES**

Bizeau, J., Tapeinos, C., Marella, C., Larrañaga, A., and Pandit, A. (2017). Synthesis and characterization of hyaluronic acid coated manganese dioxide microparticles that act as ROS scavengers. *Colloids Surf. B: Biointerfaces* 159, 30–38. doi:10.1016/j.colsurfb.2017.07.081

Boe, R. J., Lee, S. H., and Park, H. (2016). Biofunctionalized nanoparticles: an emerging drug delivery platform for various disease treatments. *Drug Discov. Today* 21, 1303–1312. doi:10.1016/j.drudis.2016.06.005

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Nikolić, M., Wagner, T., Merabet, L., et al. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* 5, 175–195. doi:10.1016/j.brs.2011.03.002

Carvalho-de-Souza, J. L., Treger, J. S., Dang, B., Kent, S. B., Pepperberg, D. R., and Bezanilla, F. (2015). Photosensitivity of neurons enabled by cell-targeted gold nanoparticles. *Neuron* 86, 207–217. doi:10.1016/j.neuron.2015.02.033

Cavallaro, G., Lazzara, G., Massaro, M., Milìoto, S., Noto, R., Parisi, F., et al. (2015). Biocompatible Poly(N-isopropylacrylamide)-halloysite nanotubes for thermo-responsive curcumin release. *J. Phys. Chem. C* 119, 8944–8951. doi:10.1021/acs.jpcc.5b00991

Chen, R., Romero, G., Christiansen, M. G., Mohr, A., and Anikeeva, P. (2015). Wireless magnetothermal deep brain stimulation. *Science* 347, 1477–1480. doi:10.1126/science.1261821

Cheng, L., Yang, K., Li, Y., Zeng, X., Shao, M., Lee, S. T., et al. (2012). Multifunctional nanoparticles for upconversion luminescence/MR multimodal imaging and
magnetically targeted photothermal therapy. *Biomaterials* 33, 2215–2222. doi:10.1016/j.biomaterials.2011.11.069

Ciofani, G., Danti, S., Genchi, G. G., Liakos, I., Cappello, V., Gemmi, M., Athanassiou, A., Danti, S., Genchi, G. G., D' Alessandro, D., Pellequer, J. L., Odorico, M., et al. (2013a). Biocompatibility of boron nitride nanotubes: an up-date of in vivo biological investigation. *Int. J. Pharm.* 44, 85–88. doi:10.1016/j.ijpharm.2013.01.037

Ciofani, G., Genchi, G. G., Liakos, I., Cappello, V., Gemmi, M., Athanassiou, A., et al. (2013b). Effects of cerium oxide nanoparticles on PC12 neuronal-like cells: proliferation, differentiation, and dopamine secretion. *Pharmacol. Res.* 63, 2133–2145. doi:10.1016/s1109-013-1071-y

Ciofani, G., Genchi, G. G., Mazzolai, B., and Mattoli, V. (2014). Transcriptional profile of genes involved in oxidative stress and antioxidant defense in PC12 cells following treatment with cerium oxide nanoparticles. *Biochim. Biophys. Acta* 1840, 495–506. doi:10.1016/j.bbabio.2013.10.009

Du, B., Han, S., Li, H., Zhao, F., Su, X., Cao, X., et al. (2015). Multi-functional boron nitride nanotube-mediated stimulation. *Int. J. Nanomedicine* 7, 19–24. doi:10.2147/IJN.S28144

Eom, K., Kim, J., Choi, J. M., Kang, T., Chang, J. W., Byun, K. M., et al. (2014). Remote control of induced dopaminergic neurons in parkinsonian rats. *J. Clin. Invest.* 124, 3215–3229. doi:10.1172/JCI74664

Eom, K., Kim, J. M., Kang, T., Chang, J. W., Byun, K. M., et al. (2014). Enhanced infrared neural stimulation using localized surface plasmon resonance of gold nanorods. *Small* 10, 3853–3857. doi:10.1002/smll.201400599

Fang, R. H., Hu, C. M., Luk, B. T., Gao, W., Copp, J. A., Tai, Y., et al. (2014). Cancer imaging and photothermal therapy in the near-infrared region by using gold nanorods. *J. Am. Chem. Soc.* 136, 2115–2120. doi:10.1021/ja506752a

Jarvis, S., and Schultz, S. R. (2015). Prospects for optogenetic augmentation of brain function. *Front. Syst. Neurosci.* 9:157. doi:10.3389/fnsys.2015.00157

Kim, H. W., Yang, K., Jeong, W. J., Choi, S. J., Lee, J. S., Cho, A. N., et al. (2016). Photovitroactivation of noncovalently assembled peptide ligands on carbon nanotubes enables the dynamic regulation of stem cell differentiation. *ACS Appl. Mater. Interfaces* 8, 26470–26481. doi:10.1021/acsami.6b06796

Krishnamurthy, S., Gnanasammandhan, M. K., Xie, C., Huang, K., Cui, M. Y., and Chan, J. M. (2016). Monocyte cell membrane-derived nanohosts for targeted cancer therapy. *Nanoscale* 8, 6981–6985. doi:10.1039/c5nr07588b

Lee, Y. S., Wu, S., Arinzeh, T. L., and Bunge, M. B. (2017). Enhanced noradrenergic axon regeneration into Schwann cell-filled PVDF-TrFE conduits after complete spinal cord transaction. *Biotechnol. Bioeng.* 114, 444–456. doi:10.1002/bit.26088

Liu, J., Liu, J., and Chen, C. (2017). Remote control and modulation of cellular events by plasmonic gold nanoparticles: implications and opportunities for biomedical applications. *ACS Nano* 11, 2403–2409. doi:10.1021/acsnano.7b01200

Lu, Y., Aimi, A. L., Ranger, R., and Ga, Z. (2016). Bioreponsive materials. *Nat. Rev. Mater.* 2, 16075. doi:10.1038/natrevmats.2016.75

Luk, B. T., and Zhang, L. (2015). Cell membrane-camouflaged nanoparticles for drug delivery. *J. Control Release* 220 (Pt B), 600–607. doi:10.1016/j.ijconrel.2015.07.019

Marino, A., Araí, S., Hou, Y., Degl'Innocenti, A., Cappello, V., Mazzolai, B., et al. (2017a). Gold nanoshell-mediated remote myocyte activation. *ACS Nano* 11, 2494–2508. doi:10.1021/acsnano.6b08202

Marino, A., Genchi, G. G., Sinibaldi, E., and Ciofani, G. (2017b). Piezoelectric effects of materials on bio-interfaces. *ACS Appl. Mater. Interfaces* 9, 17663–17680. doi:10.1021/acsami.7b04323

Miyako, E., Russier, J., Mauro, M., Cebrian, C., Yayow, H., Menard-Moyon, C., et al. (2013). Gelatin/nanoceria nanocomposite fibers as antioxidant scaffolds for neuronal regeneration. *Biochim. Biophys. Acta* 1861, 386–395. doi:10.1016/j.bbabio.2016.11.022

Miyamoto, Y. K., Panda, S. K., Jayabal, R., Sharma, N., Bastia, A. K., and Mohanta, T. K. (2017). Antimicrobial, antioxidant and cytotoxic activity of silver nanoparticles synthesized by leaf extract of *Erythrina suberosa* (Roxb.). *Front. Mol. Biosci.* 4:14. doi:10.3389/fmbiol.2017.00014
