Next Generation Nanomaterials: Smart Nanomaterials, Significance, and Biomedical Applications

15

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Abstract

Over the advancement of nanotechnology, a vast number of nanomaterials have been developed and successfully utilized in various applications. Specifically in biomedical applications, still it is a challenging to fabricate nanomaterials with good functional properties for acheiveing better therapeutics. To overcome the limitations of common nanomaterials, smart materials are grabbing more significant attention recently. In earlier days, these smart materials are often defined as a material which can respond in a timely manner to the surrounding environment. Thereafter, definition of smart materials has been expanded that the material that can stimuli by external factors and results a new kind of functional properties. Stimuli agents are further classified as light, temperature, electric, magnetic field, stress, pressure, pH, etc. These controlled abilities of smart materials make them particularly interesting to utilize in various applications such as controlled release of drugs, treatment of various diseases, biosensors, etc. So it is very important to know the various kind of smart nanomaterials and their unique properties under specific stimulating agents. Therefore, in the present chapter, we aim to show various classification of smart nanomaterials and its beneficial advantages in biomedical applications in the past to the future.

Keywords

Next-generation nanomaterials · Smart nanomaterials · Significance and biomedical applications

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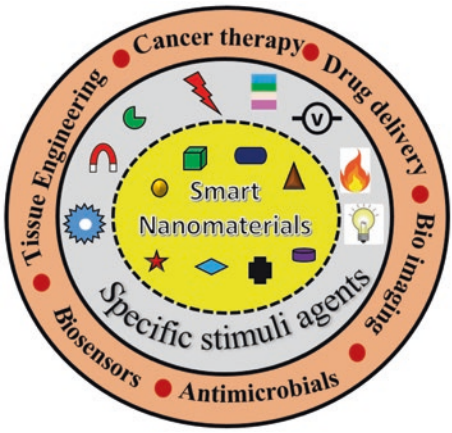

15.1 Introduction

Over the decades, nanotechnology and nanomaterials played a vital role in the development of scientific and technological disciplines. Specifically, nanomaterials such as graphene, nanotubes, metal, and polymer nanoparticles have been gaining significant attention. These nanomaterials (smaller size, ≤100 nm) exhibits an outstanding physio-chemical property such as higher molar extinction coefficients, superior reactivity, higher absorption and surface area, tunable plasmonic properties, photo and magnetic properties, and quantum effects due to their dimensions. Therefore, over the years several kinds of nanomaterials were successfully explored in various fields. Particularly, significant attention has been drawn in biomedical human health applications, where small molecules therapeutics exhibit serious disadvantages including poor photostabilities, non-biocompatible, side effects to other organs, fast renal clearance, lower retention time in blood fluids, poor targeting ability, and insufficient cellular uptake. Subsequently nanomaterials were developed and explored, even though nanomaterials offer an advantage over the small molecules still the non-controlled therapeutics make them as limiting factor. To overcome the existing challenges, recently stimuli responsive materials have drawn significant attention due to their controlled properties under specific stimuli agents and these materials are often called as smart materials.

15.1.1 What Are Smart Materials

Smart material can be defined as "materials that can change their properties according to the specific stimuli." In other words, "Materials that can change their shape, density, texture, color, modulus, rigidity, and toughness all on demand in response to specific stimuli." In earlier days, these smart materials are often defined as a material which can respond in a timely manner to the surrounding environment.

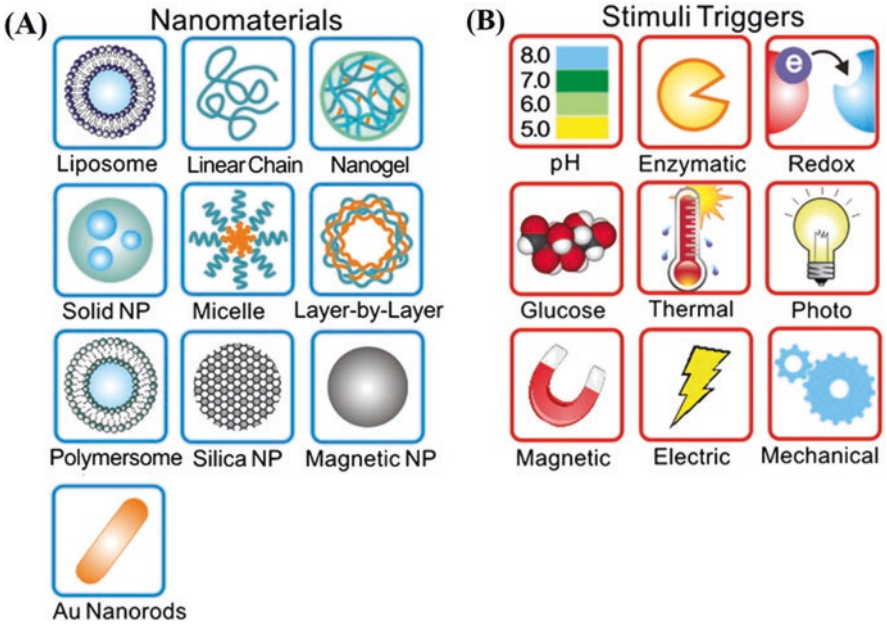

Fig. 15.1 Schematic (**a**) various classes of nanomaterials and (**b**) specific stimulating agents. Reproduced with the permission from Lu et al. (2014)

Thereafter, definition of smart materials has been expanded that the material that can be stimuli by external factors and exhibit a new kind of functional properties. Specific stimuli agents can be either temperature changes, wavelengths of light, pressure, stress, electric, magnetic field, chemical concentration, etc., while output produced can be color, heat, hyperthermia, magnetic, deformation, etc., Fig. 15.1 shows the schematic representation of various nanomaterials and corresponding stimulating agents. Under the specific stimuli, these materials can change their own properties such as changes in size, optical, mechanical properties, surface area, permeability, solubility, shape, among other nanomaterials. Basically, most of the smart materials exhibit five characteristic properties such as immediacy, transiency, self-actuation, directness, and selectivity. The immediacy is nothing but a material that can respond quickly once the stimuli appear, whereas transiency means it can react to more than one environment, and the properties depending on the specific environment. Some materials exhibit its own special internal properties, and which are not induced or produced by external actions is called as Self-actuation. Directness is that the output produced at the point of input given, so this response is local. Finally, selectivity is predictable and repeatable characteristic of the response, so a single environmental state can only lead to a unique and constant response of the material. Figure 15.2 shows the schematic representation of the response of the smart materials under specific stimuli. These results clearly reveal that how a specific morphology of a nanomaterial can change under specific stimulating agents.

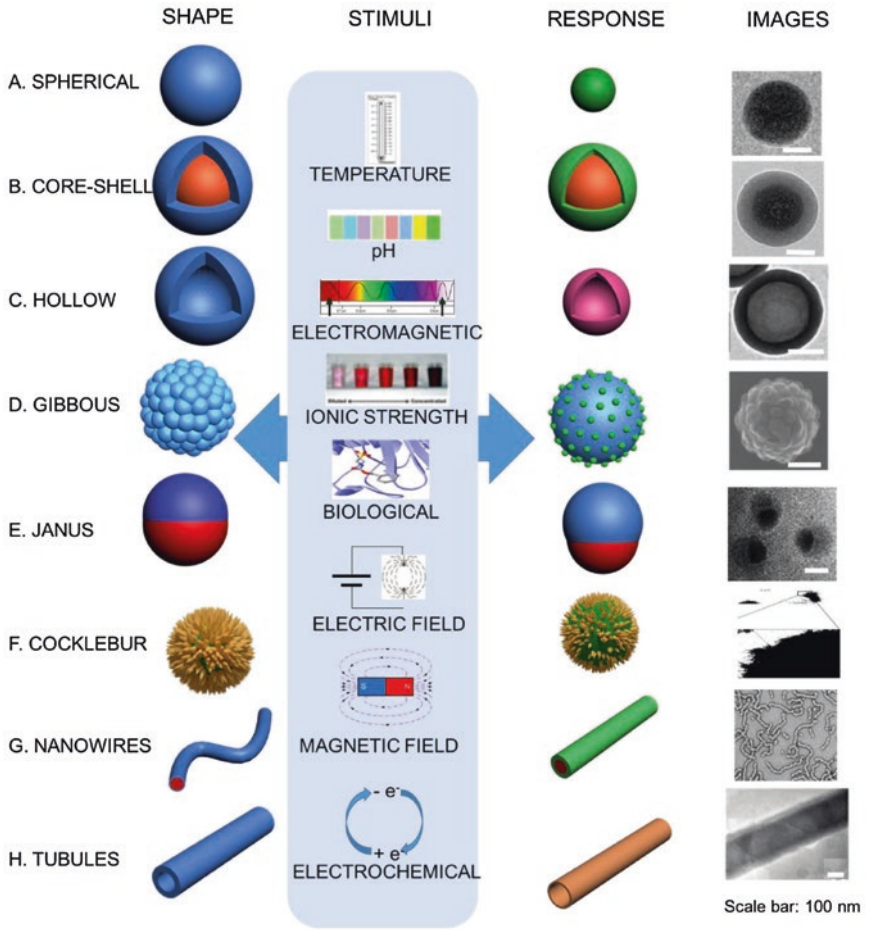

Fig. 15.2 Morphological changes of various nano-objects under specific physical or chemical stimulating agent. Reproduced with the permission from Lu and Urban (2018)

15.1.2 Smart Materials vs Common Materials

Unique, controllable and functional properties of smart materials make them fundamentally different from common materials. Most of the common materials exhibit fixed properties and change in the properties might occur by adding the new functional groups. Whereas in smart materials, these properties become viable. The materials can respond to the particular stimuli and eventually exhibit new functional properties. Another beautiful advantage of smart materials is the response that is simple and immediate, whereas response in common materials is complex, time-consuming, and complicated. However, the practical utility of smart materials is not yet studied well. Some advantages and disadvantages of smart materials are listed below.

Advantages	Disadvantages
• High energy density	• Very expensive
• Better durability and reliability	• Very sensible, proper storage needed
• Excellent bandwidth	• Not readily available
• Reduces the production cost	• Proper skill to recognize it among the other materials
• Ability to control the shape and size	• Long-term effects unknown
• Easily cooled with nanofluids	• Dropping people out of the labor
• Extensively used in textile industries	
• Reduces weight of component in mechanical and electrical industries	
• Real time health monitoring	
• Self-repairing if damage occurs	
• Simplified packing	
• Huge volume changes with respect to temperature	

Interesting and controlling properties of smart materials make them different from common materials. Further, these smart materials were classified into various groups according to the specific stimuli agents. The detailed classification is discussed below.

15.2 Classification of Smart Nanomaterials Based on Under Specific Stimuli

Smart nanomaterials are classified as various subgroups with respect to the specific stimuli response. Properties of smart materials can be significantly altered by external inputs, such as stress, temperature, moisture, pH, electric and magnetic field in a controlled manner. According to their different properties, different types of smart materials are available and some of them are discussed below: A schematic representation of various types of smart nanomaterials under different external stimuli agents is shown in Fig. 15.3.

15.2.1 Piezoelectric Smart Materials

The word "Piezoelectricity" comes from the Greek words meaning "pressure electricity." Pierre and Jacques Curie first discovered the effect of piezoelectricity in 1880. They identified the generation of spark from certain materials such as quartz. The piezoelectric material can be defined as "The materials can convert the mechanical energy to electrical energy directly under applied mechanical stress." This effect is reversible, so the electric charge also can help to generate mechanical stress and vice versa. Under the specific stimuli such as mechanical stress or electric charge, material causes asymmetric nature or changes its shape, respectively. Most

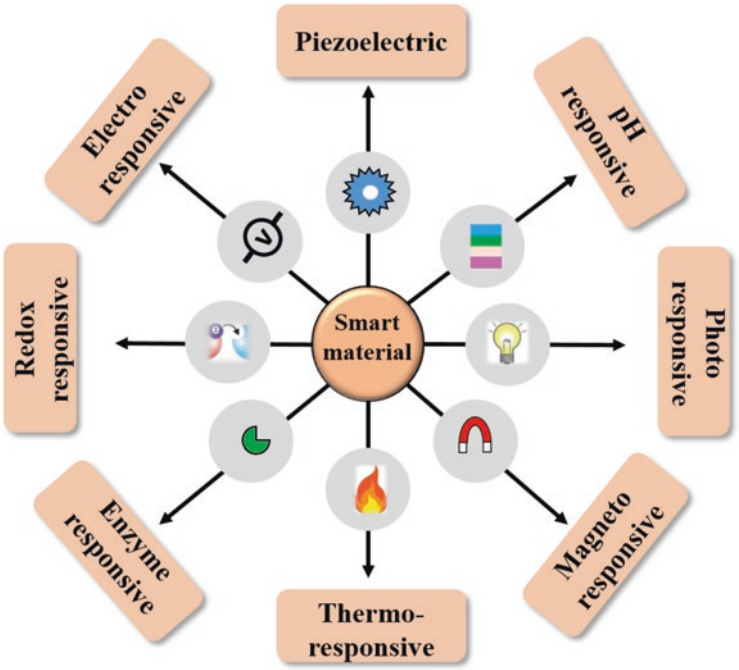

Fig. 15.3 Classification of smart materials with respect to specific stimuli

predominant materials in which we can observe the piezo-electric effects are non-conductive materials, such as SiO_2 (Quartz). Besides, ceramics also exhibit excellent piezoelectric effects. Mostly used ceramic piezoelectric material is lead zirconium titanate (PZT). These PZT materials exhibit high piezoelectric coefficients and it is very cheap to manufacture. By the principle of piezoelectricity, when a piezoelectric material is placed under stress, it creates a dipole moment by changing the balance of ions in the crystal structure (Fig. 15.4(a–d)). Most importantly, the net dipole should not be cancelled by other dipoles in the unit cell. To achieve this the atomic structure of piezoelectric crystal should be non-centrosymmetric (Chorsi et al. 2019). Furthermore, controlled properties of piezoelectricity smart nanomaterials can be useful for various industrial applications particularly those related to vibrational generation and actuation. Thereafter, many commercialized products were developed based on piezoelectricity principle that include timekeeping using quartz resonance, microphones, radio antenna oscillators, speakers, hydrophones, and fuel injection (Topolov et al. 2015). Subsequently, later the development of advanced nanotechnology, a wide variety of smart nanomaterials stimuli by piezoelectric property were developed and can be fabricated as thin films, discs, or stacked sheets. However, the serious drawback of these piezoelectric materials is degradation due to the applying of repeated forces on the piezoelectric material. However, applying repeated forces on piezoelectric devices causes degradation

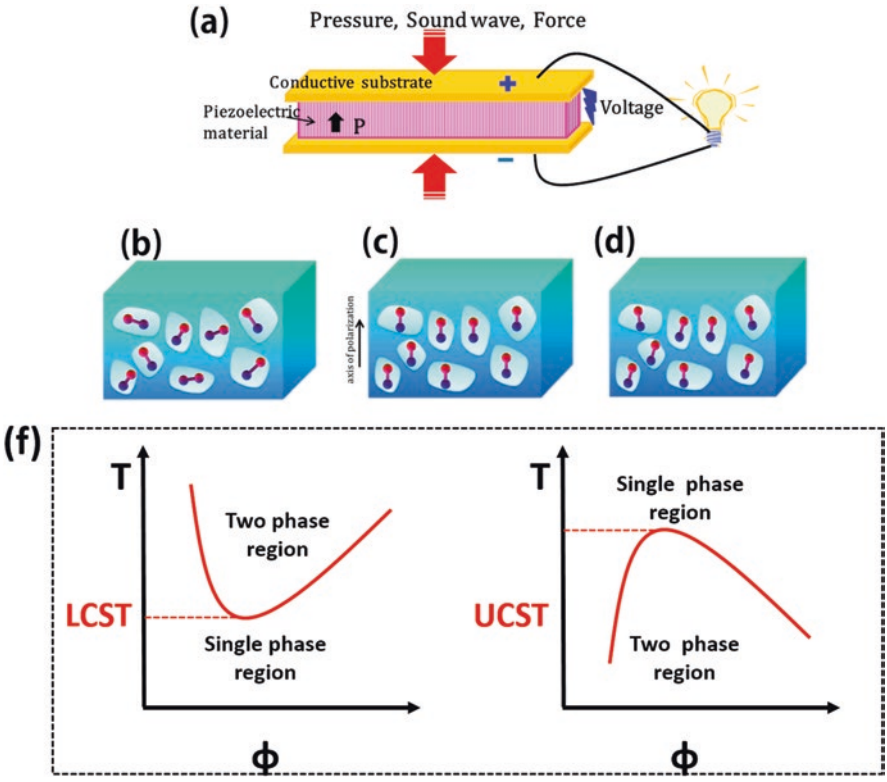

Fig. 15.4 (**a**) Working principle of piezoelectric smart material. Polarization (P) condition and directions of electrons (**b**) under without applied forces or strain (**c**) during the applied force (**d**) after the applied force removed. (**f**) The working principle of thermoresponsive smart materials of piezoelectric and thermoresponsive materials, respectively. (**a**–**d**) Reproduced with the permission from Chandrasekaran et al. (2019)

which is the main limitation so far. Thus, the design of the well-matured piezoelectric materials needs to be highly considered in future applications.

Over the advancement of nanotechnology, smart piezoelectric materials are extensively explored in human health applications. In early 400 B.C, electrotherapy is a commonly used technique in medicine to cure the neurological diseases based on electrical stimulations. As well, torpedo fishes are commonly exploited in reducing or controlling the pain on human body by producing electric shocks (of ~100 to 150 V). Subsequently, the advancement of knowledge and nanotechnology is able to store the electricity in batteries. Therefore, electrical stimulation of tissues gained more attention in the 1800s and development of piezoelectric materials was advanced. Notably, cell and tissues highly responsive to the applied electric fields even inside the cells. Thus, this uniqueness is extremely exciting and opening the new era to develop piezoelectric materials for clinical use. Subsequently, nanostructured piezoelectric interfaces play a vital role in nanomedicine for cell and tissue stimulation. Rather

Table 15.1 Applications and characteristics of some Piezoelectric materials in biomedical applications

S. no.	Smart material	Characteristics	Application	Ref.
1	Poly(vinylidene fluoride) (PVDF)	Flexible, cheap, respiratory sensor	Monitoring human respiratory conditions	Liu et al. (2017b)
2	PDMS-SWNT	Fast response time, high stability, low detectable pressure	Monitor wrist pulse, muscle movement	Wang et al. (2014)
3	FSKNG	Highly durable, ultrasensitive, fast response	Monitor arterial pulses, vocal cord vibration, and gentle wrist movements	Ghosh and Mandal (2017)
4	Collagen films	Biocompatible, biodegradable protein	Temperature sensor, strain gauge, etc.	Moreno et al. (2015)
5	rGO/PVDF microdome array	Tactile sensitivities ultra-minute detections	Dynamic pressure sensor, temperature sensor	Park et al. (2015)
6	Fibrous scaffolds	Promoting chondrogenic and osteogenic differentiation	Human mesenchymal stem cell differentiation and tissue formation	Damaraju et al. (2017)
7	Boron nitride nanotube	Superior resistance to chemical and temperature	Excitation of neuron-like cells	Ciofani et al. (2010)
8	Barium titanate NPs	Biocompatibility, high dielectric constant	Stimulation of SH-SY5Y-derived neurons	Marino et al. (2015)
9	PZT nanoribbons	Minimally invasive, sensitive, scalable platform	To detect minute cellular deformations	Nguyen et al. (2012)
10	Enzyme/ZnO nanoarrays	Real time, sensitive	Biosensing	Han et al. (2017)

than passive structural units or carriers for medications, smart properties of piezoelectric devices are gaining more attention. Besides, stretchable, flexible, and cost-effective wearable e-skins of Piezoelectric smart materials are promising tools for the prevention of illnesses, health monitoring, Human physiological monitoring, and the prediction of early diseases. In addition, piezoelectric materials also can be used to promote disease healing by systematic studies of these materials on body. At the present stage, exact reason and mechanism of piezoelectric materials are not yet fully discovered but studies into the bone related injuries show that induced electric fields can accelerate the bone repair and growth of neurons (Rajabi et al. 2015). Table 15.1 shows the utilization of some piezoelectric polymer smart nanomaterials in various biomedical applications. "Despite the impressive potential of piezoelectric nanostructures in biomedical field, further research efforts are still necessary for the evaluation of the nanomaterial biocompatibility, retention, degradability, accumulation in complex in vivo systems before actual exploitation in clinical context."

15.2.2 Electrochromic and Photochromic Smart Materials

At first, electrochromism is the phenomenon where the color or opacity of a material changes when a voltage is applied. Mainly reversible change in optical properties (such as absorbance, reflectance, transmittance, etc.) of material was observed under applied voltage. Since the discovery of electrochromism (EC), synthesis of EC materials gained considerable progress and the principle mechanism is as follows. It mainly involves the ions insertion/extraction into/out of EC materials. As expected, an efficient ion insertion/extraction process takes place in nanostructured materials due to the larger surface area. Therefore, several organic, inorganic, and polymer materials exhibit electrochromism properties which include viologens (Cinnsealach et al. 1998), polyaniline (PANI) (Gospodinova and Terlemezyan 1998), organic polymers and metal oxides materials (Yoo et al. 2007; Wu and Yang 2007; Cheng et al. 2006). In inorganic materials, cathodic coloration under negative potentials and bleaching states under positive potentials were observed (WO_3, TiO_2, $V2O_5$ films, etc). It is mainly due to the charge balancing ions (H^+, Li^+, Na^+, K^+ ions) and insertion/extraction of electrons accompanied by the reduction/oxidation reactions (Niklasson and Granqvist 2007). Whereas coloration under positive potentials was observed in case of nickel iridium oxide. Further, unique advantages of EC materials have been extended in various interesting applications that include antiglare mirrors, smart windows, displays, and active camouflages (Wang et al. 2010). Among all, application of EC materials in smart windows stands as a potential application where they can save energy and provide indoor comfort by reversible color changes. These electrochromic materials in a biomedical application are rarely reported.

In a similar way like electrochromism, photochromism (PC) can be defined as color change of materials that occur under photon energy. Notably, these photochromic materials exhibit a reversible change in their color with respect to the specific photon energy. It was discovered in the late 1880s by Markwald and they discovered in reversible change of color of 2,3,4,4-tetrachloronaphthalen-1(4*H*)-one in the solid state. In the early days this new phenomenon labeled as phototropy and this name was used until the 1950s. Subsequently, the name was changed to photochromism. Photochromism can take place in both organic, inorganic compounds and also in biological systems. Owing to its phenomenal properties of photochromic materials, further explored in sensors and fast optical shutters applications. In health applications, PC materials are extensively used in ophthalmic sun screening applications and in UV light protection glasses. As well, in cooling glasses these PC materials were used and when exposed to sunlight these materials turn to darken and reverse back to colorless for personal comfort and safety (Christie 2013).

15.2.3 Thermoresponsive Smart Materials

Thermoresponsive polymers are a class of "smart" materials that can respond to a change in temperature; a property that makes them useful materials in a wide range

of applications and consequently attracts much scientific interest. The theory of thermoresponsive polymer (similarly, microgels) began in the 1940s with work from Flory and Huggins who both independently produced similar theoretical expectations for polymer in solution with varying temperature.

The main principle involved in the thermoresponsive materials are as follows and these types of thermoresponsive properties are mostly observed in polymeric materials. According to the principle, there are two main types of polymers such as lower critical solution temperature (LCST) and the second one is an upper critical solution temperature (UCST). In fact, the solubility of polymer in aqueous solution depends on several factors such as temperature, molecular weight, co-solvent, etc. As shown in Fig. 15.4(f), we can identify the critical solution temperature easily if the phase diagram of polymer mixture vs temperature exhibits the one- or two-phase region. Critical temperature points of LCST and UCST are shown below and above, respectively, in where the solvent and polymer are completely miscible. So therefore, if the polymer solution below the LCST is a clear and homogeneous solution whereas above the LCST is cloudy (which also called cloud point). It mainly happens because it is energetically favorable (Ward and Georgiou 2011). Importantly, the main reason for favorable phase separation by increasing the temperature is mainly because of entropy of the system according to the Gibbs equation $\Delta G = \Delta H - T\Delta S$ (G: Gibbs free energy, H: enthalpy, and S: entropy).

As a proof of concept, several synthetic methodologies are successfully employed to produce various kinds of thermoresponsive smart materials that include free radical copolymerization, end-group functionalization, sol-gel transition phase method, copolymerization, self-assembly method, photopolymerization, etc. (Kim and Matsunaga 2017). By utilizing the unique advantages of smart materials, further explored in biomedical applications such as drug delivery, gene delivery and tissue engineering, etc. In drug delivery, numerous polymer/nanomaterials-based platforms were successfully utilized in the delivery of cancer drugs on the target site to achieve a massive therapeutic effect. The main key factors in sustainable delivery of drugs are needed to deliver drugs on right time, at the right area, and at right concentrations where many systems have a serious problem to achieve this. The main problems associated with the existing systems are enzyme degradations, low solubility of drugs, non-specific toxicity, fast clearance rates from the body, and inability to cross the biological barriers (Juillerat-Jeanneret 2008). To overcome this obstacle several nanocarriers-based polymers have been used (Liechty et al. 2010). However, it is very difficult to control the drug release rate on that specific nanocarriers because the concentration of drug on target site is either lower or higher. Subsequently, controlled properties of the thermoresponsive smart materials are used to deliver the drugs. These smart carriers can be able to deliver the drugs at a right time and right concentration by simply controlling with external stimuli. Table 15.2 shows some thermoresponsive smart materials in biomedical applications. On the other hand, Gene therapy aims at the treatment of many genetic diseases by correcting the defective genes that are responsible for diseases. To this end, several strategies have been employed to deliver the specific genes such as viruses, polymer carriers, etc. Even though having its own merits, serious stability issues

Table 15.2 Applications and characteristics of some thermoresponsive materials in biomedical applications

S. no.	Smart material	Characteristics	Application	Ref.
1	PCEC	High gel strength, slow degradation	Drug release	Zhou et al. (2017)
2	PNIPAM-PDMA-PAA	Tunable properties	Drug delivery	Chen et al. (2018)
3	AuNPs-PF127-HPMC	Extended release, biodegradability, excellent safety profile	Drug delivery, photothermal platform, skin wound healing	Arafa et al. (2018)
4	PEO-PPO-PEO	Solubility, stability, release, and bioavailability of drugs	Sustained release of drugs, oral drug delivery. Release of nitric oxide for accelerating wound healing	Liu et al. (2017a)
5	Poly(NAGA-co-BA)	Loading of doxorubicin and IcG	Drug delivery, bioimaging	Hui et al. (2016)
6	Pluronic	Injectable, thermos responsive	Drug delivery	Jung et al. (2017)
7	NiPAAm	Injectable, long-term absorption, multifunctional sensing	Biomolecule carriers wound healing, sensing, imaging	Pentlavalli et al. (2017), Wu et al. (2018), Wang et al. (2011)
8	Poly(*N*-isopropylacrylamide) s (PNIPAAM)	Biocompatibility, low levels of toxicity	Oral and insulin delivery, hemostasis	Gandhi et al. (2015)
9	TMC-g-PNIPAAm	Minimal cytotoxicity	Gene carrier	Mao et al. (2007)
10	PDMAPAAm–PNIPAM 4	High payloads of DNA	Gene transfection	Zhou et al. (2007)

of polymers makes them as a limited for practical applications. So therfore, developing a new carrier systems for successful gene delivery is highly desired. Interestingly, thermoresponsive polymers stand as potential candidates to enhance the gene transfection efficiency by changing the temperature either during the complexation and/or during the incubation or transfection period defective genes that are responsible for these genetic diseases. In particular, some studies were revealed that polymer based PNIPAAm, linear and branched NIPAAm, DMAEMA, and PEI polymers exhibits better and enhanced transfection efficiency. As well, tissue engineering is an emerging topic towards restoring or improvement of tissue function by developing the biological substitutes (Sponchioni et al. 2019). Thermoresponsive smart polymer materials are commonly used in tissue engineering to enable cell growth and proliferation. Especially, these thermoresponsive materials can facilitate cell–cell interactions

and further facilitate their use for regenerative therapies by creating thick tissues with stacking methods. Whereas three-dimensional thermoresponsive platforms give the opportunity to control tissue geometries in a 3-D manner by mimicking the native tissue architecture and enable their further retrieval. It is still challenging to preserve their functionalities for a long time (Tekin et al. 2011). Table 15.2 shows the utilization of some thermoresponsive polymer smart nanomaterials in various biomedical applications.

15.2.4 pH Dependent Smart Materials

pH stimuli smart materials can be defined as the material which can respond to the pH and exhibit new functional properties. Over the last decade, tremendous efforts have been made in the development of pH-responsive biomaterials along with other stimuli (temperature, etc.) responsive materials for targeted site-specific therapeutic applications. In general, different components of human body have different pH levels, for example, the pH of saliva is 6.5–7.5; whereas upper and lower parts of stomach have pH values of 4–6.5 and 1.5–4.0, respectively. Also, pathological state exhibits abnormal pH values compared to physiological state pH, for instance, bacterial infections contain acidic pus with pH of 6.0–6.6, the tumor microenvironment exhibits a lower extracellular pH in the range of 6.5–6.9, and an inflamed tissue exhibits pH in the range of 6–7. Based on these unique pH variations, various pH-responsive materials have been developed so far. As a proof of concept, several pH-responsive materials can be synthesized by incorporating (a) protonatable groups (amino, sulfonates, imidazolyl, and carboxyl groups) containing polymers such as polysaccharides (e.g., chitosan, etc.) and polypeptides (e.g., poly(*l*-histidine, etc.) that undergo pH-responsive solubility and/or conformational changes or (b) polymers carrying acid labile bonds (e.g., hydrazine, imine, oxime, ketal, acetal, orthoester, thiopropionate, vinyl ester, etc.) whose cleavage allows the release of molecules or the modification of the surface charge.

Several pH dependent polymers were addressed. For example, Chitosan, a polysaccharide with many primary amino groups in its polymeric backbone, is widely used for the development of pH-responsive biomaterials (Sultankulov et al. 2019). It possesses amino groups with pKa of 6.5; therefore, chitosan and its-derivative based biomaterials exhibit positive surface charge under pathological milieu (acidic condition) due to protonation of amino groups and neutral/negative surface charge in physiological milieu (neutral pH). Under pathological conditions, the positively charged chitosan materials readily adhere to negatively charged cell surfaces through electrostatic interactions so they can be used to target and provide site-specific therapeutic efficacy thereby excrete possible adverse effects. Recently, Yan et al. developed a pH-responsive glycol chitosan coated liposome system for tumor specific drug delivery. The coated liposomes exhibited negative-to-positive charge reversion from pH 7.4 to pH 6.5 which mediated cellular uptake, and thus higher antitumor efficiency was observed due to the more accumulation of DOX in the tumor cells compared to the free drug or conventional liposomes (Yan et al. 2015).

More recently, polyaniline conjugated glycol chitosan nanoparticles were developed to cause aggregation of bacteria in pathological milieu and by this means confine therapeutic effect to the focal infection (Korupalli et al. 2017). Another example, Poly-*l*-histidine (PLH), a pH-responsive imidazole groups (pKa = 6.0–6.5) containing cationic polypeptide, has also been widely used in the design of pH-responsive materials for drug delivery and other biomedical applications (Jiang et al. 2012). Under acidic conditions the protonated imidazole moiety leads to the phase transition from lipophilic to hydrophilic and causes the release of encapsulated drugs via the destabilization of PLH containing polymeric nanocarriers. Otherwise, the positively charged PLH produces a positive surface charge on the surface of PLH based materials and facilitates strong interactions with the negatively charged cell walls/tissues through electrostatic-mediated binding. The aforementioned advantages of PLH guided to the development of pH-responsive surface charge switching poly(*d*,*l*-lactic-co-glycolic acid)-*b*-PLH-*b*-poly(ethylene glycol) (PLGA-PLH-PEG) micelle nanoparticles for bacteria targeting antibiotic drug delivery. The results of NP binding studies demonstrated that PLGA-PLH-PEG NPs adhered to bacteria under conditions of acidity (Radovic-Moreno et al. 2012).

Likewise, insertion of acid labile chemical bonds in the polymer is another strategy to design pH-responsive materials. The cleavage of the chemical bonds under pathological acidic milieu has gained much attention in biomedical applications particularly in the field of the drug delivery systems for targeted and site-specific drug delivery (Kanamala et al. 2016). The rate-determining step for pH-responsive bond cleavage is acid-catalyzed hydrolysis, which can be modulated by choosing appropriate linkers. The most used pH-sensitive linkers for this purpose include imine, hydrazone, Polyacetal and polyketal, oxime, amide, ether, and orthoester bonds. In one of the studies, Yang et al. synthesized pH-responsive polymeric conjugates by covalently bonding between PEG with 4β-aminopodophyllotoxin (NPOD) via imine linkage for tumor cell specific paclitaxel delivery (Kang et al. 2014). The mPEG-NPOD conjugates exhibited faster release of NPOD under acidic conditions compared to physiological pH conditions. Sun et al. conjugated Doxorubicin (DOX) to gold nanoparticles via hydrazone bonds to facilitate pH-responsive DOX release in tumor cells (Sun et al. 2014). In vitro studies demonstrated that the acid labile bond cleavage enabled the intracellular DOX release to cancer cells. Tomlinson et al. synthesized amino-functionalized linear pH-sensitive polyacetals to form water soluble polyacetal-DOX conjugates (Tomlinson et al. 2003). In vivo biodistribution studies in mice bearing tumors confirmed two-fold enhancement in the half-life of polyacetal-DOX conjugates compared to control (HPMA-DOX conjugates). These pH-sensitive conjugates not only exhibited less deposition of DOX in the liver and spleen and increased accumulation in tumor.

Following concerns are necessary to improve the better pH dependent smart nanomaterials for an efficient therapeutics and diagnosis, as follows:

1. Appropriate sizes of nanocarriers are necessary for enhancing the retention time, avoiding undesirable clearance and accumulation in tumor specific cells via EPR effect.

Table 15.3 Applications and characteristics of some pH dependent materials in biomedical applications

S. no.	Smart material	Characteristics	Application	Ref.
1	HyUPS nanotransistors	Multi-pH sensing capability	Receptor-mediated endocytosis in tumor cells	Wang et al. (2017)
2	LDH-ZnPcS8 nanohybrid	Photosensitizer delivery, minimal phototoxicity	PDT	Li et al. (2017)
3	AuNPs	Fast, ultrasensitive, quick aggregation, more uptake	PTT	Liu et al. (2013)
4	PDPA-b-PAMA/SA	Targeting, high retention	Drug release	Wu et al. (2014b)
5	MelNP	Physical aggregation	Photoacoustic (PA) imaging	Ju et al. (2016)
6	PPC-Hyd-DOX-DA	Dual pH sensor	Drug delivery	Du et al. (2011)
7	PDPA-b-PAMA/DMMA	Rapid cell endocytosis, long blood circulation, targeting	Drug release	Wu et al. (2014a)
8	$LNPde_{PEG\text{-}FA}$	Nucleus targeting	Drug delivery	Fan et al. (2016)
9	PEG[(PLG/PEI)/DNA]	Dual charge/size, long retention	Gene delivery	Guan et al. (2016)
10	cRGD-PCM/DOX NPs	Quick drug release, long circulation, targeting	Drug delivery	Liu et al. (2016b)

2. In some of the tumors such as CT26 colon tumor which has high permeability nature so that pH-responsive aggregation-based nanocarriers in slightly acidic pH tumor environment can promote more uptake.
3. Whereas for poorly permeable tumors such as the BXPC-3 pancreatic tumor, cellular uptake can be accelerated by using pH dependent size shrinkage nanocarriers via escaping from lysosomes and endosomes to deliver the drug to nucleus.
4. After successful internalization of nanocarriers by tumor cells, required dose of drug need to be released from pH-responsive nanocarrier to induce the cell apoptosis.
5. Programmable size changes of pH-dependent nanocarriers are useful for tumor imaging and diagnosis.

Utilization of some pH-responsive smart nanomaterials in various biomedical applications is shown in Table 15.3. Even though significant efforts have been made in pH-responsive materials still some challenges exist. Some of the challenges are poor penetration in deep tumors, nano carrier's aggregation in tumor microenvironment, varying tumor vascular leakage by changing pore diameter, unpredictable tumor environment due to the rapid mutations, etc.

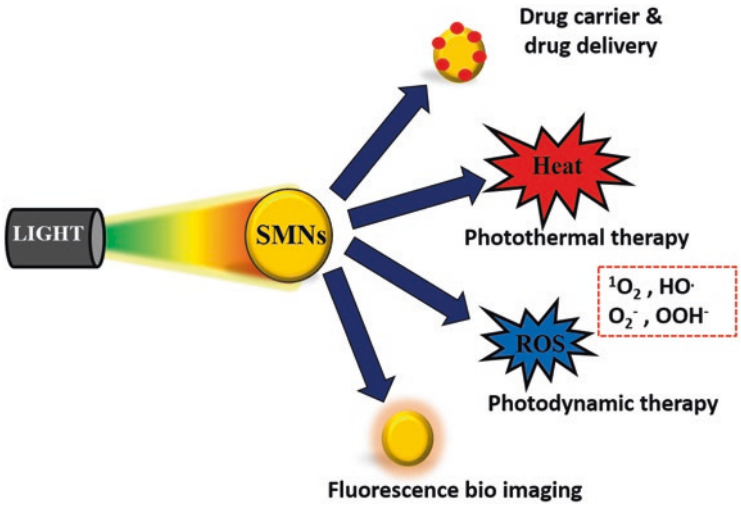

Fig. 15.5 Mechanism of light responsive smart nanomaterials

15.2.5 Photoresponsive Smart Materials

Photoresponsive smart materials can be defined as materials that can respond to the external light. Specifically, controlled properties and non-invasiveness of photo-triggered smart nanomaterials are playing very important role to achieve efficient therapeutics. Whereas other internal stimuli such as temperature, pH dependent, enzyme activity, glutathionine concentration have some serious limitations in tumor biology. For example, most of the pH in tumor environment is 6.5 so that we cannot use beyond that and high temperature is 40–42 °C, overexpression of antioxidants as well as various enzyme overexpression (e.g., cathepsin, matrix metalloproteinases, plasminogen activators) compared to normal tissue can effectively minimize the therapeutic effects. To overcome these limitations, external stimuli agents such as ultrasound, magnetic field, and light responsive drug delivery systems stand as a potential candidate. To the proof of concept, many drug delivery systems were successfully utilized and proved that can effectively control the drug release by external stimuli when compared to internal stimuli (Raza et al. 2019). Among the all external stimuli, light is considered as an attractive external stimulus due to its tunable and controllable properties. In addition, light responsive smart materials also can be used as a biomarker to track the targeting ability, location of drugs, and visualize the tumors by optical imaging techniques. As shown in Fig. 15.5, there are three main types of photo-triggered theranostics, namely photoactivation of chemotherapeutics, photodynamic, and photothermal activation. First, photoactivation of small molecule to deliver the drugs to cure the non-curable diseases is a fascinating challenge. However, difficulties in the synthesis of drug carriers, non-controlled drug release and inter-individual variability as a limiting factor in many existing drug delivery systems(Liu et al. 2016a). To conquer the problems associated with the

drug delivery systems, light mediated chemotherapeutics by using smart nanomaterials such as polymers/nanomaterials is an alternative way where we can control the drug delivery on target sites and can be able to deliver the drugs with right concentration in a right time. Subsequently, several light responsive smart materials were successfully employed for drug delivery but unfortunately most of them respond to UV light which has few disadvantages like poor tissue penetration and harmful to normal tissues. Therfore, UV light responsive drug delivery systems are not useful for practical applications. To overcome the limitations, further NIR light responsive smart materials for drug delivery systems were developed which have deep tissue penetration due to lesser attenuation and also safer for tissues. Second, photodynamic therapy uses light and photoabsorbing chemical substance to produce the reactive oxygen species such as peroxide, hydroxyl, singlet oxygen, etc. which can effectively stimulate the cellular mediations to kill cancer/bacteria cell. Noticeably, photodynamic therapeutic systems require low levels of laser powers to generate the cytotoxic reactive oxygen species at interested area/regions is pivotal for its efficiency. In a conventional way, many photodynamic systems were successfully utilized the organic photosensitizers (such as Porphyrin, chlorin Ce_6, etc.) to mediate the photodynamic effects but unfortunately photobeaching, poor solubility, lower molar extinction coefficients make limiting factors (Lan et al. 2019). As well, most of the photosensitizers are only activated in UV/vis region which may cause the potential light toxicity and limited tissue penetration. To overcome these challenges, photoresponsive smart nanomaterials drag a significant attention where these materials can effectively generate the reactive oxygen species, good water solubility, targeting ability as well as near infrared light activation makes them as potential agents to overcome deep tissue problems (Vankayala and Hwang 2018). Third, photothermal therapy is killing of cancer/bacteria cells by local hyperthermia generated on light activated photoabsorbing materials. In biological environments, the generated overheated media may cause several hazardous effects such as protein aggregation and denaturation, evaporation of cytosol, and cell lysis for living cells. As mentioned earlier, most of the recent phototherapeutic platforms effectively utilize the NIR responsive smart nanomaterials/polymers to overcome the drawbacks associated with photosensitizers as well as UV/vis light responsive fluorophores (Thangudu et al. 2020). Besides, recently there are many efforts made to visualize the deep tissue cancer tumors by NIR fluorescence imaging in a broad biological window region where several NIR fluorophores and nanomaterials were explored and still exploring rapidly (Deng et al. 2018). Table 15.4 shows the utilization of some photoresponsive smart nanomaterials in various biomedical applications.

In the future, in order to achieve an efficient phototherapeutic platform on nanomaterials-based systems, following requirements are very important to create a better therapeutic platform:

1. Light absorption: Particularly in phototherapeutic platforms, photocatalyst should absorb light absorption cross sections in broad biological window wave-

Table 15.4 Applications and characteristics of some photoresponsive smart materials in biomedical applications

S. no.	Smart material	Characteristics	Application	Ref.
1	Ce_6-MNPs	ROS species under 632 nm light	In vivo PDT	Huang et al. (2011)
2	Poly-Ru	ROS species under 660 nm	In vivo PDT and Photochemotherapy	Sun et al. (2017)
3	DPP-TI, DPP-TIH and DPP-r-TI.	ROS and heat generation under 660 nm	In vivo PDT and PTT	Yang et al. (2017)
4	Ultrathin black phosphorus nanosheets	ROS under 660 nm	In vivo PDT	Wang et al. (2015)
5	NaYF4:Yb, Er@ $mSiO_2$@ Fe_3O_4-PEG NPs	Fluorescence imaging under 980 nm, drug carrier	In vivo bioimaging drug release	Liu et al. (2015)
6	EuGdOx@MSF	ROS, drug carrier under 980 nm	In vivo PDT, drug delivery, fluorescence imaging	Kalluru et al. (2016)
7	Copper sulfide	Heat under NIR lasers	In vivo PTT	Marin et al. (2018)
8	SWCNTs	Imaging under 785 nm	In vivo NIR fluorescence imaging	Yudasaka et al. (2017)
9	Au NEs	ROS and heat under 808, 980, 1064 nm	In vivo PTT and PDT	Vijayaraghavan et al. (2014)
10	Polymers	Heat under NIR lasers	In vivo PTT	Pierini et al. (2018)

length regions. Therefore, it would facilitate the large light to heat conversion efficiencies (Albota et al. 1998).

2. Low toxicity: Nanomaterials should not be toxic to the healthy cells. This is necessary to achieve selective treatments with minimum side effects (Teeguarden et al. 2006).
3. Easy functionalization: Surface functionalization is necessary to improve the cancer specific cell targeting which allows accumulation of high load of nanomaterials drug to improve the phototherapeutics (Nikolic et al. 2006).
4. Biocompatibility: It is necessary to minimize the side effects on other organs. So the nanomaterials must have long circulation times and high retention time in the bloodstream (Choi et al. 2006).

15.2.6 Electroresponsive Smart Materials

Electroresponsive materials are materials that respond to an applied electric field by changing their size or shape. These new class of materials attracted rapidly due to their potential applications in various fields such as sensors, optical systems,

actuators, robotics, artificial muscles, drug delivery, and energy harvesting applications. Briefly, electroresponsive materials were divided into two types mainly. First one is the ionic electroresponsive materials in which mobility of ions induced by electric field to create a change in the local concentration of the ions in materials or solution. It mainly occurs in conductive polymers, ion polymers, and polymer-metal composites. Second one includes the dielectric elastomers and electrostrictive polymers. Particularly in biomedical applications, controlled release of drugs and accumulation on electroresponsive nanoparticle drug carries such as polymers and microgels are interesting. For example, electroresponsive materials were assembled with poly(ethylene imine) with a ferrocene end-group and encapsulated pyrene. On applying a small electric field, oxidation of ferrocene and further hydrophobic nature to hydrophilic nature transition results from the release of encapsulated drug (Sun et al. 2013). The unique redox properties of the electroresponsive material can be a potential candidate for an electrocontrolled release of drugs to treat the various diseases. Importantly, release of drugs can control the erosion of gels and electrochemical treatment. Even though having its own merits, relatively high voltage and a long-time electrical potential treatment limit their applications.

15.2.7 Magnetoresponsive Smart Materials

The development of magnetic nanomaterials has been proved to be extremely beneficial advantages in whole industrial and commercial applications such as photonic, electronic devices, magnetic storage, and biomedical theranostics. It can be defined as "Magnetoresponsive materials are materials that can respond to an applied magnetic field as a stimuli agent." Particularly, magnetic NPs (MNPs) are an emerging platform and paying more attention for their magnetic responsive based applications in biomedical field such as magnetic hyperthermia, magnetic resonance imaging (MRI) and magnetic guided drug delivery owing to its unique intrinsic chemical and physical properties. These magnetic responsive materials have been successfully synthesized by various techniques includes hydrothermal process, co-precipitation method, chemical vapor deposition, combustion, carbon arc, laser pyrolysis, electrochemical synthesis, high temperature thermal decomposition, microbial synthesis, etc. (Cardoso et al. 2018). First in magnetic hyperthermia, traditionally thermotherapy used to kill the cancer cells by increasing the local region/whole body temperature to 42–45 °C using microwaves, ultrasounds. Other way is by thermal ablation, applying a temperature above 45 °C to the diseased area. However, these traditional methods suffer from poor targeting ability and deep tissue penetration (Habash et al. 2007). Subsequently, magnetic NPs mediated hyperthermia for targeting the specific cancers have been developed (Mahmoudi et al. 2018). Where the magnetic properties of the MNPs in the fluid take the advantages of applied magnetic field and efficiently convert into heat. Even though development of promising magnetic hyperthermia therapies for treatment of cancer but still in infancy and more preclinical and clinical developments needed for before the practical use. Second, Magnetic Resonance Imaging (MRI) is a versatile tool and

useful in clinical diagnostics for many diseases which offers a real time spatial resolution and higher contrast of soft tissues without side effects. The principle relies on alignment of protons within a sample under applied external magnetic field. Clinically Gadolinium based chelating agents are extensively utilized as a MRI contrast agent to visualize the tumor diagnosis (Shen et al. 2015). However, economic, high contrast ability agents needed to replace the existing agents. Therefore, to further improve the signal to background noise ratio, various T1 weighted and T2 weighted contrast agents were developed. For example, Several MNPs such as gadolinium, iron, and non-iron based NPs systems were successfully employed as a MRI contrast agent (Perlman and Azhari 2018). Despite the several advantages of MRI, delayed imaging rate and accuracy, sensitivity and toxicity in some contrast media is still a serious issues. Therefore, more attention and efforts are required to improve the current MRI technologies for future biomedical applications. Third in magnetic induced drug delivery, several magnetic NPs were successfully utilized in controlled release of drugs to target tissue. In the future, the following requirements are very important to develop a magnetoresponsive material for the better therapeutic platform:

1. Degradation of some Nobel metal contrast agent's results decreases the image quality. Therefore, stable nanomaterials need to be developed.
2. High contrast ability with less cytotoxicity materials should be needed
3. None of the Radiation techniques are specific to tumors alone which may cause critical damage to other organs
4. In addition, advancement of the instrumentation that is capable to enhance and control the magnetic field is highly needed to increase the utility of magnetic responsive smart nanomaterials.

15.3 Current Trends in Smart Nanomaterials

As discussed in the chapter, significant advances achieved on design and synthesis of various smart materials with respective to specific stimuli but still some concerns need to be improved for better future applications. First, serious drawback of piezoelectric materials is degradation due to the applying of repeated forces on the piezoelectric material. Thus, design of the well matured piezoelectric materials needs to be highly considered in future applications. As well, future thermoresponsive smart materials could be applied into chronic diseases such as diabetes which needed regular doses of drug. Programmable size changes of pH-dependent nanocarriers are useful for tumor imaging and diagnosis in future biomedical applications. In photoresponsive smart materials, broad biological window region NIR absorption photoresponsive smart nanomaterials are needed to develop for deep tumor therapeutics and fluorescence imaging. Over the advancement of smart materials, recently dual or multiresponsive stimuli smart materials for efficient therapeutics have gained significant attention. As compared to single stimuli responsive smart materials, multi-stimuli responsive materials offer more functions and finer

Table 15.5 Dual or multistimuli responsive smart materials and applications

S1. No.	Smart material	Stimuli response	Application	Ref.
1	PLA-g-P(NIPAAm-co-MAA) NPs	pH and thermo	Drug carriers and release	Lo et al. (2005)
2	DS-g-PEG/cRGD nanoparticles	pH and redox	Nucleus targeted drug delivery	K. C et al. (2012)
3	Fe_3O_4-capped MSNs	pH and magnetic	Drug delivery	Gan et al. (2011)
4	DNA-capped MSNs	T and enzyme	Controlled drug delivery	Chen et al. (2011)
5	Azo-PDMAEMA	Light/pH/T	Controlled drug release	Tang et al. (2010)
6	PMAAS–S@Fe_3O_4 microcontainers	pH/redox/ magnetic	Drug carrier, hyperthermia, imaging	Bilalis et al. (2012)
7	P(NIPAAm-co-MAA) coated magnetic MSNs	T/pH/ magnetic	Drug delivery	Chang et al. (2011)
8	S-NPs@DOX	pH/redox/T	Drug delivery	Yu et al. (2018)
9	MFNPs	pH/ magnetic,	Targeting, drug delivery, MR imaging	Bhattacharya et al. (2016)
10	rGO-PDA Nano sheets	Light /pH	Drug delivery, phototherapy	Jiang et al. (2018)

modulations can be achieved through more parameters. As a result, utilization of some dual and multistimuli responsive smart nanomaterials in various biomedical applications were employed with effective therapeutic outcomes (Table 15.5). Importantly, clearance and accumulation of nanomaterials in non-targeted locations such as liver, kidney, and spleen are major problems in therapeutic diagnostics. It is mainly due to the fact that most of the nanomaterials fail to adequately overcome biological barriers. Therefore, more focus should be needed to develop nanomaterials to overcome the biological barriers efficiently to minimize the side effects of nanodrugs. Overall, smart, flexible, efficient and multiresponsive stimuli on a single site smart nanomaterial (all in one platform) are highly interested in future applications.

15.4 Conclusions

In conclusion, overall significant efforts have been achieved in the design and synthesis of the various kind of smart nanomaterials for biomedical applications such as drug delivery, bioimaging of cancer specific cells, tissue engineering and cancer, bacteria therapeutics, etc. Present smart materials can offer beautiful abilities like controlled therapeutics by tuning the specific stimuli agents to enhance the therapeutic efficiencies. To further improve the disease diagnosis dual or multiresponsive smart materials are paying more attention recently where we can trigger the multiple functions on a single smart nanomaterial. As well, in the present chapter we also

discussed the advantages and limitations of smart nanomaterials in biological applications which helps to construct the novel, stable, and efficient smart materials for future applications. Finally, we strongly envision that present discussions in this chapter will help to understand the abilities of various kinds of smart nanomaterials and develop a more advanced smart material platform for future biomedical applications for better human health.

References

Albota MA, Xu C, Webb WW (1998) Two-photon fluorescence excitation cross sections of biomolecular probes from 690 to 960 nm. Appl Opt 37(31):7352–7356. https://doi.org/10.1364/AO.37.007352

Arafa MG, El-Kased RF, Elmazar MM (2018) Thermoresponsive gels containing gold nanoparticles as smart antibacterial and wound healing agents. Sci Rep 8(1):13674. https://doi.org/10.1038/s41598-018-31895-4

Bhattacharya D, Behera B, Sahu SK, Ananthakrishnan R, Maiti TK, Pramanik P (2016) Design of dual stimuli responsive polymer modified magnetic nanoparticles for targeted anti-cancer drug delivery and enhanced MR imaging. New J Chem 40(1):545–557. https://doi.org/10.1039/C5NJ02504D

Bilalis P, Chatzipavlidis A, Tziveleka L-A, Boukos N, Kordas G (2012) Nanodesigned magnetic polymer containers for dual stimuli actuated drug controlled release and magnetic hyperthermia mediation. J Mater Chem 22(27):13451–13454. https://doi.org/10.1039/C2JM31392H

Cardoso VF, Francesko A, Ribeiro C, Bañobre-López M, Martins P, Lanceros-Mendez S (2018) Advances in magnetic nanoparticles for biomedical applications. Adv Healthc Mater 7(5):1700845. https://doi.org/10.1002/adhm.201700845

Chandrasekaran S, Bowen C, Roscow J, Zhang Y, Dang DK, Kim EJ, Misra RDK, Deng L, Chung JS, Hur SH (2019) Micro-scale to nano-scale generators for energy harvesting: self-powered piezoelectric, triboelectric and hybrid devices. Phys Rep 792:1–33. https://doi.org/10.1016/j.physrep.2018.11.001

Chang B, Sha X, Guo J, Jiao Y, Wang C, Yang W (2011) Thermo and pH dual responsive, polymer shell coated, magnetic mesoporous silica nanoparticles for controlled drug release. J Mater Chem 21(25):9239–9247. https://doi.org/10.1039/C1JM10631G

Chen C, Geng J, Pu F, Yang X, Ren J, Qu X (2011) Polyvalent nucleic acid/Mesoporous silica nanoparticle conjugates: dual stimuli-responsive vehicles for intracellular drug delivery. Angew Chem Int Ed 50(4):882–886. https://doi.org/10.1002/anie.201005471

Chen Y, Gao Y, da Silva LP, Pirraco RP, Ma M, Yang L, Reis RL, Chen J (2018) A thermo-/pH-responsive hydrogel (PNIPAM-PDMA-PAA) with diverse nanostructures and gel behaviors as a general drug carrier for drug release. Polym Chem 9(29):4063–4072. https://doi.org/10.1039/C8PY00838H

Cheng K-C, Chen F-R, Kai J-J (2006) V2O5 nanowires as a functional material for electrochromic device. Sol Energy Mater Sol Cells 90(7):1156–1165. https://doi.org/10.1016/j.solmat.2005.07.006

Choi J-S, Jun Y-W, Yeon S-I, Kim HC, Shin J-S, Cheon J (2006) Biocompatible Heterostructured nanoparticles for multimodal biological detection. J Am Chem Soc 128(50):15982–15983. https://doi.org/10.1021/ja066547g

Chorsi MT, Curry EJ, Chorsi HT, Das R, Baroody J, Purohit PK, Ilies H, Nguyen TD (2019) Piezoelectric biomaterials for sensors and actuators. Adv Mater 31(1):1802084. https://doi.org/10.1002/adma.201802084

Christie RM (2013) 1—Chromic materials for technical textile applications. In: Gulrajani ML (ed) Advances in the dyeing and finishing of technical textiles. Woodhead Publishing, pp 3–36. https://doi.org/10.1533/9780857097613.1.3

Cinnsealach R, Boschloo G, Nagaraja Rao S, Fitzmaurice D (1998) Electrochromic windows based on viologen-modified nanostructured TiO2 films. Sol Energy Mater Sol Cells 55(3):215–223. https://doi.org/10.1016/S0927-0248(98)00096-8

Ciofani G, Danti S, D'Alessandro D, Ricotti L, Moscato S, Bertoni G, Falqui A, Berrettini S, Petrini M, Mattoli V, Menciassi A (2010) Enhancement of Neurite outgrowth in neuronal-like cells following boron nitride nanotube-mediated stimulation. ACS Nano 4(10):6267–6277. https://doi.org/10.1021/nn101985a

Damaraju SM, Shen Y, Elele E, Khusid B, Eshghinejad A, Li J, Jaffe M, Arinzeh TL (2017) Three-dimensional piezoelectric fibrous scaffolds selectively promote mesenchymal stem cell differentiation. Biomaterials 149:51–62. https://doi.org/10.1016/j.biomaterials.2017.09.024

Deng G, Li S, Sun Z, Li W, Zhou L, Zhang J, Gong P, Cai L (2018) Near-infrared fluorescence imaging in the largely unexplored window of 900-1,000 nm. Theranostics 8(15):4116–4128. https://doi.org/10.7150/thno.26539

Du J-Z, Du X-J, Mao C-Q, Wang J (2011) Tailor-made dual pH-sensitive polymer–doxorubicin nanoparticles for efficient anticancer drug delivery. J Am Chem Soc 133(44):17560–17563. https://doi.org/10.1021/ja207150n

Fan Y, Li C, Li F, Chen D (2016) pH-activated size reduction of large compound nanoparticles for in vivo nucleus-targeted drug delivery. Biomaterials 85:30–39. https://doi.org/10.1016/j.biomaterials.2016.01.057

Gan Q, Lu X, Yuan Y, Qian J, Zhou H, Lu X, Shi J, Liu C (2011) A magnetic, reversible pH-responsive nanogated ensemble based on Fe3O4 nanoparticles-capped mesoporous silica. Biomaterials 32(7):1932–1942. https://doi.org/10.1016/j.biomaterials.2010.11.020

Gandhi A, Paul A, Sen SO, Sen KK (2015) Studies on thermoresponsive polymers: phase behaviour, drug delivery and biomedical applications. Asian Journal of Pharmaceutical Sciences 10(2):99–107. https://doi.org/10.1016/j.ajps.2014.08.010

Ghosh SK, Mandal D (2017) Sustainable energy generation from piezoelectric biomaterial for noninvasive physiological signal monitoring. ACS Sustain Chem Eng 5(10):8836–8843. https://doi.org/10.1021/acssuschemeng.7b01617

Gospodinova N, Terlemezyan L (1998) Conducting polymers prepared by oxidative polymerization: polyaniline. Prog Polym Sci 23(8):1443–1484. https://doi.org/10.1016/S0079-6700(98)00008-2

Guan X, Guo Z, Lin L, Chen J, Tian H, Chen X (2016) Ultrasensitive pH triggered charge/size dual-rebound gene delivery system. Nano Lett 16(11):6823–6831. https://doi.org/10.1021/acs.nanolett.6b02536

Habash RWY, Bansal R, Krewski D, Alhafid HT (2007) Thermal therapy. Part III: Ablation Techniques 35(1–2):37–121. https://doi.org/10.1615/CritRevBiomedEng.v35.i1-2.20

Han W, He H, Zhang L, Dong C, Zeng H, Dai Y, Xing L, Zhang Y, Xue X (2017) A self-powered wearable noninvasive electronic-skin for perspiration analysis based on Piezo-biosensing unit matrix of enzyme/ZnO Nanoarrays. ACS Appl Mater Interfaces 9(35):29526–29537. https://doi.org/10.1021/acsami.7b07990

Huang P, Li Z, Lin J, Yang D, Gao G, Xu C, Bao L, Zhang C, Wang K, Song H, Hu H, Cui D (2011) Photosensitizer-conjugated magnetic nanoparticles for in vivo simultaneous magnetofluorescent imaging and targeting therapy. Biomaterials 32(13):3447–3458. https://doi.org/10.1016/j.biomaterials.2011.01.032

Hui L, Qin S, Yang L (2016) Upper critical solution temperature polymer, Photothermal agent, and erythrocyte membrane coating: an unexplored recipe for making drug carriers with spatiotemporally controlled cargo release. ACS Biomater Sci Eng 2(12):2127–2132. https://doi.org/10.1021/acsbiomaterials.6b00459

Jiang T, Zhang Z, Zhang Y, Lv H, Zhou J, Li C, Hou L, Zhang Q (2012) Dual-functional liposomes based on pH-responsive cell-penetrating peptide and hyaluronic acid for tumor-targeted anticancer drug delivery. Biomaterials 33(36):9246–9258. https://doi.org/10.1016/j.biomaterials.2012.09.027

Jiang W, Mo F, Lin Y, Wang X, Xu L, Fu F (2018) Tumor targeting dual stimuli responsive controllable release nanoplatform based on DNA-conjugated reduced graphene oxide for

chemo-photothermal synergetic cancer therapy. J Mater Chem B 6(26):4360–4367. https://doi.org/10.1039/C8TB00670A

Ju K-Y, Kang J, Pyo J, Lim J, Chang JH, Lee J-K (2016) pH-induced aggregated melanin nanoparticles for photoacoustic signal amplification. Nanoscale 8(30):14448–14456. https://doi.org/10.1039/C6NR02294D

Juillerat-Jeanneret L (2008) The targeted delivery of cancer drugs across the blood–brain barrier: chemical modifications of drugs or drug-nanoparticles? Drug Discov Today 13(23):1099–1106. https://doi.org/10.1016/j.drudis.2008.09.005

Jung Y-S, Park W, Park H, Lee D-K, Na K (2017) Thermo-sensitive injectable hydrogel based on the physical mixing of hyaluronic acid and Pluronic F-127 for sustained NSAID delivery. Carbohydr Polym 156:403–408. https://doi.org/10.1016/j.carbpol.2016.08.068

Kalluru P, Vankayala R, Chiang C-S, Hwang KC (2016) Unprecedented "all-in-one" lanthanide-doped Mesoporous silica frameworks for fluorescence/MR imaging and combination of NIR light triggered chemo-photodynamic therapy of Tumors. Adv Funct Mater 26(43):7908–7920. https://doi.org/10.1002/adfm.201603749

Kanamala M, Wilson WR, Yang M, Palmer BD, Wu Z (2016) Mechanisms and biomaterials in pH-responsive tumour targeted drug delivery: a review. Biomaterials 85:152–167. https://doi.org/10.1016/j.biomaterials.2016.01.061

Kang Y, Ha W, Liu Y-Q, Ma Y, Fan M-M, Ding L-S, Zhang S, Li B-J (2014) pH-responsive polymer–drug conjugates as multifunctional micelles for cancer-drug delivery. Nanotechnology 25(33):335101. https://doi.org/10.1088/0957-4484/25/33/335101

KC RB, Thapa B, Xu P (2012) pH and redox dual responsive nanoparticle for nuclear targeted drug delivery. Mol Pharm 9(9):2719–2729. https://doi.org/10.1021/mp300274g

Kim Y-J, Matsunaga YT (2017) Thermo-responsive polymers and their application as smart biomaterials. J Mater Chem B 5(23):4307–4321. https://doi.org/10.1039/C7TB00157F

Korupalli C, Huang C-C, Lin W-C, Pan W-Y, Lin P-Y, Wan W-L, Li M-J, Chang Y, Sung H-W (2017) Acidity-triggered charge-convertible nanoparticles that can cause bacterium-specific aggregation in situ to enhance photothermal ablation of focal infection. Biomaterials 116:1–9. https://doi.org/10.1016/j.biomaterials.2016.11.045

Lan M, Zhao S, Liu W, Lee C-S, Zhang W, Wang P (2019) Photosensitizers for photodynamic therapy. Adv Healthc Mater 8(13):1900132. https://doi.org/10.1002/adhm.201900132

Li X, Zheng B-Y, Ke M-R, Zhang Y, Huang J-D, Yoon J (2017) A tumor-pH-responsive Supramolecular photosensitizer for Activatable photodynamic therapy with minimal in vivo skin Phototoxicity. Theranostics 7(10):2746–2756. https://doi.org/10.7150/thno.18861

Liechty WB, Kryscio DR, Slaughter BV, Peppas NA (2010) Polymers for Drug Delivery Systems. Annual Review of Chemical and Biomolecular Engineering 1(1):149–173. https://doi.org/10.1146/annurev-chembioeng-073009-100847

Liu X, Chen Y, Li H, Huang N, Jin Q, Ren K, Ji J (2013) Enhanced retention and cellular uptake of nanoparticles in Tumors by controlling their aggregation behavior. ACS Nano 7(7):6244–6257. https://doi.org/10.1021/nn402201w

Liu B, Li C, Ma P, Chen Y, Zhang Y, Hou Z, Huang S, Lin J (2015) Multifunctional NaYF4:Yb, Er@mSiO2@Fe3O4-PEG nanoparticles for UCL/MR bioimaging and magnetically targeted drug delivery. Nanoscale 7(5):1839–1848. https://doi.org/10.1039/C4NR05342G

Liu D, Yang F, Xiong F, Gu N (2016a) The smart drug delivery system and its clinical potential. Theranostics 6(9):1306–1323. https://doi.org/10.7150/thno.14858

Liu J, Liu Q, Yang C, Sun Y, Zhang Y, Huang P, Zhou J, Liu Q, Chu L, Huang F, Deng L, Dong A, Liu J (2016b) cRGD-modified Benzimidazole-based pH-responsive nanoparticles for enhanced tumor targeted doxorubicin delivery. ACS Appl Mater Interfaces 8(17):10726–10736. https://doi.org/10.1021/acsami.6b01501

Liu Y, Yang F, Feng L, Yang L, Chen L, Wei G, Lu W (2017a) In vivo retention of poloxamer-based in situ hydrogels for vaginal application in mouse and rat models. Acta Pharm Sin B 7(4):502–509. https://doi.org/10.1016/j.apsb.2017.03.003

Liu Z, Zhang S, Jin YM, Ouyang H, Zou Y, Wang XX, Xie LX, Li Z (2017b) Flexible piezoelectric nanogenerator in wearable self-powered active sensor for respiration and healthcare monitoring. Semicond Sci Technol 32(6):064004. https://doi.org/10.1088/1361-6641/aa68d1

Lo C-L, Lin K-M, Hsiue G-H (2005) Preparation and characterization of intelligent core-shell nanoparticles based on poly(d,l-lactide)-g-poly(N-isopropyl acrylamide-co-methacrylic acid). J Control Release 104(3):477–488. https://doi.org/10.1016/j.jconrel.2005.03.004

Lu C, Urban MW (2018) Stimuli-responsive polymer nano-science: shape anisotropy, responsiveness, applications. Prog Polym Sci 78:24–46. https://doi.org/10.1016/j.progpolymsci.2017.07.005

Lu Y, Sun W, Gu Z (2014) Stimuli-responsive nanomaterials for therapeutic protein delivery. J Control Release 194:1–19. https://doi.org/10.1016/j.jconrel.2014.08.015

Mahmoudi K, Bouras A, Bozec D, Ivkov R, Hadjipanayis C (2018) Magnetic hyperthermia therapy for the treatment of glioblastoma: a review of the therapy's history, efficacy and application in humans. Int J Hyperth 34(8):1316–1328. https://doi.org/10.1080/02656736.2018.1430867

Mao Z, Ma L, Yan J, Yan M, Gao C, Shen J (2007) The gene transfection efficiency of thermoresponsive N,N,N-trimethyl chitosan chloride-g-poly(N-isopropylacrylamide) copolymer. Biomaterials 28(30):4488–4500. https://doi.org/10.1016/j.biomaterials.2007.06.033

Marin R, Skripka A, Besteiro LV, Benayas A, Wang Z, Govorov AO, Canton P, Vetrone F (2018) Highly efficient copper Sulfide-based near-infrared Photothermal agents: exploring the limits of macroscopic heat conversion. Small 14(49):1803282. https://doi.org/10.1002/smll.201803282

Marino A, Arai S, Hou Y, Sinibaldi E, Pellegrino M, Chang Y-T, Mazzolai B, Mattoli V, Suzuki M, Ciofani G (2015) Piezoelectric nanoparticle-assisted wireless neuronal stimulation. ACS Nano 9(7):7678–7689. https://doi.org/10.1021/acsnano.5b03162

Moreno S, Baniasadi M, Mohammed S, Mejia I, Chen Y, Quevedo-Lopez MA, Kumar N, Dimitrijevich S, Minary-Jolandan M (2015) Biocompatible collagen films as substrates for flexible implantable electronics. Advanced Electronic Materials 1(9):1500154. https://doi.org/10.1002/aelm.201500154

Nguyen TD, Deshmukh N, Nagarah JM, Kramer T, Purohit PK, Berry MJ, McAlpine MC (2012) Piezoelectric nanoribbons for monitoring cellular deformations. Nat Nanotechnol 7(9):587–593. https://doi.org/10.1038/nnano.2012.112

Niklasson GA, Granqvist CG (2007) Electrochromics for smart windows: thin films of tungsten oxide and nickel oxide, and devices based on these. J Mater Chem 17(2):127–156. https://doi.org/10.1039/B612174H

Nikolic MS, Krack M, Aleksandrovic V, Kornowski A, Förster S, Weller H (2006) Tailor-made ligands for biocompatible nanoparticles. Angew Chem Int Ed 45(39):6577–6580. https://doi.org/10.1002/anie.200602209

Park J, Kim M, Lee Y, Lee HS, Ko H (2015) Fingertip skin–inspired microstructured ferroelectric skins discriminate static/dynamic pressure and temperature stimuli. Sci Adv 1(9):e1500661. https://doi.org/10.1126/sciadv.1500661

Pentlavalli S, Chambers P, Sathy BN, O'Doherty M, Chalanqui M, Kelly DJ, Haut-Donahue T, McCarthy HO, Dunne NJ (2017) Simple radical polymerization of poly(alginate-graft-N-Isopropylacrylamide) injectable Thermoresponsive hydrogel with the potential for localized and sustained delivery of stem cells and bioactive molecules. Macromol Biosci 17(11):1700118. https://doi.org/10.1002/mabi.201700118

Perlman O, Azhari H (2018) MRI and ultrasound imaging of nanoparticles for medical diagnosis. In: Kumar CSSR (ed) Nanotechnology characterization tools for biosensing and medical diagnosis. Springer, Berlin, Heidelberg, pp 333–365. https://doi.org/10.1007/978-3-662-56333-5_8

Pierini F, Nakielski P, Urbanek O, Pawłowska S, Lanzi M, De Sio L, Kowalewski TA (2018) Polymer-based Nanomaterials for Photothermal therapy: from light-responsive to multifunctional Nanoplatforms for synergistically combined technologies. Biomacromolecules 19(11):4147–4167. https://doi.org/10.1021/acs.biomac.8b01138

Radovic-Moreno AF, Lu TK, Puscasu VA, Yoon CJ, Langer R, Farokhzad OC (2012) Surface charge-switching polymeric nanoparticles for bacterial Cell Wall-targeted delivery of antibiotics. ACS Nano 6(5):4279–4287. https://doi.org/10.1021/nn3008383

Rajabi AH, Jaffe M, Arinzeh TL (2015) Piezoelectric materials for tissue regeneration: a review. Acta Biomater 24:12–23. https://doi.org/10.1016/j.actbio.2015.07.010

Raza A, Hayat U, Rasheed T, Bilal M, Iqbal HMN (2019) "Smart" materials-based near-infrared light-responsive drug delivery systems for cancer treatment: a review. J Mater Res Technol 8(1):1497–1509. https://doi.org/10.1016/j.jmrt.2018.03.007

Shen Y, Goerner FL, Snyder C, Morelli JN, Hao D, Hu D, Li X, Runge VM (2015) T1 Relaxivities of gadolinium-based magnetic resonance contrast agents in human whole blood at 1.5, 3, and 7 T. Investig Radiol 50(5):330–338. https://doi.org/10.1097/rli.0000000000000132

Sponchioni M, Capasso Palmiero U, Moscatelli D (2019) Thermo-responsive polymers: applications of smart materials in drug delivery and tissue engineering. Mater Sci Eng C 102:589–605. https://doi.org/10.1016/j.msec.2019.04.069

Sultankulov B, Berillo D, Sultankulova K, Tokay T, Saparov A (2019) Progress in the development of chitosan-based biomaterials for tissue engineering and regenerative medicine. Biomol Ther 9(9):470

Sun Y-X, Ren K-F, Zhao Y-X, Liu X-S, Chang G-X, Ji J (2013) Construction of redox-active multilayer film for electrochemically controlled release. Langmuir 29(35):11163–11168. https://doi.org/10.1021/la402378g

Sun T-M, Wang Y-C, Wang F, Du J-Z, Mao C-Q, Sun C-Y, Tang R-Z, Liu Y, Zhu J, Zhu Y-H, Yang X-Z, Wang J (2014) Cancer stem cell therapy using doxorubicin conjugated to gold nanoparticles via hydrazone bonds. Biomaterials 35(2):836–845. https://doi.org/10.1016/j.biomaterials.2013.10.011

Sun W, Li S, Häupler B, Liu J, Jin S, Steffen W, Schubert US, Butt H-J, Liang X-J, Wu S (2017) An Amphiphilic ruthenium Polymetallodrug for combined photodynamic therapy and Photochemotherapy in vivo. Adv Mater 29(6):1603702. https://doi.org/10.1002/adma.201603702

Tang X, Liang X, Gao L, Fan X, Zhou Q (2010) Water-soluble triply-responsive homopolymers of N,N-dimethylaminoethyl methacrylate with a terminal azobenzene moiety. J Polym Sci A Polym Chem 48(12):2564–2570. https://doi.org/10.1002/pola.24034

Teeguarden JG, Hinderliter PM, Orr G, Thrall BD, Pounds JG (2006) Particokinetics in vitro: Dosimetry considerations for in vitro nanoparticle toxicity assessments. Toxicol Sci 95(2):300–312. https://doi.org/10.1093/toxsci/kfl165

Tekin H, Sanchez JG, Tsinman T, Langer R, Khademhosseini A (2011) Thermoresponsive platforms for tissue engineering and regenerative medicine. AICHE J 57(12):3249–3258. https://doi.org/10.1002/aic.12801

Thangudu S, Kalluru P, Vankayala R (2020) Preparation, cytotoxicity, and in vitro bioimaging of water soluble and highly fluorescent palladium Nanoclusters. Bioengineering 7(1):20

Tomlinson R, Heller J, Brocchini S, Duncan R (2003) Polyacetal−doxorubicin conjugates designed for pH-dependent degradation. Bioconjug Chem 14(6):1096–1106. https://doi.org/10.1021/bc030028a

Topolov VY, Bowen CR, Bisegna P (2015) New aspect-ratio effect in three-component composites for piezoelectric sensor, hydrophone and energy-harvesting applications. Sensors Actuators A Phys 229:94–103. https://doi.org/10.1016/j.sna.2015.03.025

Vankayala R, Hwang KC (2018) Near-infrared-light-Activatable nanomaterial-mediated Phototheranostic Nanomedicines: an emerging paradigm for Cancer treatment. Adv Mater 30(23):1706320. https://doi.org/10.1002/adma.201706320

Vijayaraghavan P, Liu C-H, Vankayala R, Chiang C-S, Hwang KC (2014) Designing multi-branched gold Nanoechinus for NIR light activated dual modal photodynamic and Photothermal therapy in the second biological window. Adv Mater 26(39):6689–6695. https://doi.org/10.1002/adma.201400703

Wang JM, Sun XW, Jiao Z (2010) Application of nanostructures in Electrochromic materials and devices: recent Progress. Materials 3(12):5029–5053

Wang D, Liu T, Yin J, Liu S (2011) Stimuli-responsive fluorescent poly(N-isopropylacrylamide) microgels Labeled with Phenylboronic acid moieties as multifunctional Ratiometric probes

for glucose and temperatures. Macromolecules 44(7):2282–2290. https://doi.org/10.1021/ma200053a

Wang X, Gu Y, Xiong Z, Cui Z, Zhang T (2014) Silk-Molded flexible, ultrasensitive, and highly stable electronic skin for monitoring human physiological signals. Adv Mater 26(9):1336–1342. https://doi.org/10.1002/adma.201304248

Wang H, Yang X, Shao W, Chen S, Xie J, Zhang X, Wang J, Xie Y (2015) Ultrathin black phosphorus Nanosheets for efficient singlet oxygen generation. J Am Chem Soc 137(35):11376–11382. https://doi.org/10.1021/jacs.5b06025

Wang Y, Wang C, Li Y, Huang G, Zhao T, Ma X, Wang Z, Sumer BD, White MA, Gao J (2017) Digitization of Endocytic pH by hybrid ultra-pH-sensitive Nanoprobes at single-organelle resolution. Adv Mater 29(1):1603794. https://doi.org/10.1002/adma.201603794

Ward MA, Georgiou TK (2011) Thermoresponsive polymers for biomedical applications. Polymers 3(3):1215–1242

Wu M-S, Yang C-H (2007) Electrochromic properties of intercrossing nickel oxide nanoflakes synthesized by electrochemically anodic deposition. Appl Phys Lett 91(3):033109. https://doi.org/10.1063/1.2759270

Wu W, Chen M, Wang J, Zhang Q, Li S, Lin Z, Li J (2014a) Nanocarriers with dual pH-sensitivity for enhanced tumor cell uptake and rapid intracellular drug release. RSC Adv 4(58):30780–30783. https://doi.org/10.1039/C4RA05270F

Wu W, Zhang Q, Wang J, Chen M, Li S, Lin Z, Li J (2014b) Tumor-targeted aggregation of pH-sensitive nanocarriers for enhanced retention and rapid intracellular drug release. Polym Chem 5(19):5668–5679. https://doi.org/10.1039/C4PY00575A

Wu D-Q, Zhu J, Han H, Zhang J-Z, Wu F-F, Qin X-H, Yu J-Y (2018) Synthesis and characterization of arginine-NIPAAm hybrid hydrogel as wound dressing: in vitro and in vivo study. Acta Biomater 65:305–316. https://doi.org/10.1016/j.actbio.2017.08.048

Yan L, Crayton SH, Thawani JP, Amirshaghaghi A, Tsourkas A, Cheng Z (2015) A pH-responsive drug-delivery platform based on glycol chitosan–coated liposomes. Small 11(37):4870–4874. https://doi.org/10.1002/smll.201501412

Yang J, Cai Y, Zhou Y, Zhang C, Liang P, Zhao B, Shao J, Fu N, Huang W, Dong X (2017) Highly effective thieno[2,3-b]indole-diketopyrrolopyrrole near-infrared photosensitizer for photodynamic/photothermal dual mode therapy. Dyes Pigments 147:270–282. https://doi.org/10.1016/j.dyepig.2017.08.023

Yoo SJ, Lim JW, Sung Y-E, Jung YH, Choi HG, Kim DK (2007) Fast switchable electrochromic properties of tungsten oxide nanowire bundles. Appl Phys Lett 90(17):173126. https://doi.org/10.1063/1.2734395

Yu B, Song N, Hu H, Chen G, Shen Y, Cong H (2018) A degradable triple temperature-, pH-, and redox-responsive drug system for cancer chemotherapy. J Biomed Mater Res A 106(12):3203–3210. https://doi.org/10.1002/jbm.a.36515

Yudasaka M, Yomogida Y, Zhang M, Tanaka T, Nakahara M, Kobayashi N, Okamatsu-Ogura Y, Machida K, Ishihara K, Saeki K, Kataura H (2017) Near-infrared Photoluminescent carbon nanotubes for imaging of Brown fat. Sci Rep 7(1):44760. https://doi.org/10.1038/srep44760

Zhou Y-M, Ishikawa A, Okahashi R, Uchida K, Nemoto Y, Nakayama M, Nakayama Y (2007) Deposition transfection technology using a DNA complex with a thermoresponsive cationic star polymer. J Control Release 123(3):239–246. https://doi.org/10.1016/j.jconrel.2007.08.026

Zhou T, Li X, Li G, Tian T, Lin S, Shi S, Liao J, Cai X, Lin Y (2017) Injectable and thermosensitive TGF-β1-loaded PCEC hydrogel system for in vivo cartilage repair. Sci Rep 7(1):10553. https://doi.org/10.1038/s41598-017-11322-w