Smart Nanomaterials for Biomedical Applications

Subjects: Nanoscience & Nanotechnology

Contributor: Magdalena Aflori

Recent advances in nanotechnology have forced the obtaining of new materials with multiple functionalities. Due to their reduced dimensions, nanomaterials exhibit outstanding physio-chemical functionalities: increased absorption and reactivity, higher surface area, molar extinction coefficients, tunable plasmonic properties, quantum effects, and magnetic and photo properties. However, in the biomedical field, it is still difficult to use tools made of nanomaterials for better therapeutics due to their limitations (including non-biocompatible, poor photostabilities, low targeting capacity, rapid renal clearance, side effects on other organs, insufficient cellular uptake, and small blood retention), so other types with controlled abilities must be developed, called “smart” nanomaterials.

Keywords: smart nanomaterials ; stimuli-responsive polymers ; biomedical applications

1. Introduction

From the oldest times, humanity has tried to mimic nature in the way that living organisms adapt their behavior to environmental conditions to improve survival. It is well known that living systems from nature can dynamically change their properties in a smart way for adapting to the surrounding environment. Some examples are given by the *Mimosa pudica* plant which responds to stimuli such as temperature and light by undergoing a change in leaf direction [1]; by pinecones [2], wheat awn [3], and orchid tree seedpods [4] which adopt different shapes, responding to the changing environmental humidity; and by the *Venus flytrap* [5] which is able to capture insects by rapidly closing its leaves, among many others [6] [7]. The powerful abilities of the biological systems abovementioned in converting energy and executing multiple tasks inspired the researchers to develop “stimuli-responsive” materials with biomimetic behavior and a high potential of use in smart or intelligent devices.

To our knowledge, the first complete report of “intelligent materials” defined as “the materials that respond to environmental changes at the most optimum condition and manifest their own functions according to these changes” was made by Toshinori Takagi in April 1990 [8]. At that time, the coverage and the achievability of this concept was not comprehensible, but it was anticipated to open an unused field in science and innovation [9]. Nowadays, the term “intelligent material” is synonymous with “stimuli-responsive material” or “smart material” and has gained a growing interest in researchers’ concerns due to the development of advanced technologies and the increased need for new materials that meet the new requirements.

Richard Feynman, laureate of the Nobel Prize, was the first to introduce, in 1959, the nanotechnology concept. He had a revolutionary vision in a lecture entitled: “Why can’t we write the entire 24 volumes of the Encyclopedia Britannica on the head of a pin?” [10]. The term “nanotechnology” was used and defined in 1974, by Norio Taniguchi, as “nanotechnology mainly consists of the processing of separation, consolidation, and deformation of materials by one atom or one molecule” [11]. In 1997–1998, the perception of nanotechnology was more a “science fiction” vision, still being far from the practical applications [12], but in the early 2000s, nanomaterials were intensively studied and finally utilized in practice. As the field of biomedical engineering is developing new insights, the demand for highly functionalized biomaterials is increasing. Despite the astonishing diversity and complexity of living systems, they all share the possibility to react to environmental changes, crucial for maintaining normal functions. This need for adaptation has led to the development of smart nanomaterials, defined as materials that can react to a large variety of stimuli by adapting their own properties such as shape, surface area, size, permeability, solubility, mechanical properties, and others. Depending on the capacity of the nanomaterial to restore its initial state, the response can be reversible or not. In this specific situation, polymer-based materials have substantiated themselves as sharp choices in creating upgraded responsive frameworks on the grounds that their structure permits regulating their properties. A large variety of polymers have been obtained to respond to physical stimuli (temperature, light, ultrasound, electrical, magnetic, mechanical), chemical stimuli (pH, solvent, electrochemical), or biological stimuli (enzymes). A special type of polymer is dual or multi-stimuli-responsive, in light of the fact that it simultaneously reacts to multiple stimuli. As a rule, the polymer responsivity is directed by the science of the monomers and their distribution/concentration in the polymer chains [13].

2. Types of Stimuli

Smart nanomaterials are categorized in different groups by means of the applied stimuli. The properties of smart nanomaterials are modified by external triggers in a controlled way [14][15][16][17][18][19][20][21][22]. By considering their various properties, many kinds of smart nanomaterials are known.

2.1. Physico-Responsive Nanomaterials

Examples of physico-sensitive nanomaterials and their applications are listed in Table 1 [24][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38]. Recent works [41-76] describe the design of phisico-responsive smart nanomaterials and their applications in the biomedical field.

Table 1. Examples of physico-responsive nanomaterials and their biomedical applications.

Nr. Crt.	Stimuli	Nanomaterial	Application	Reference
1.	Temperature	*Poly(ethylene oxide)$_a$-poly(propylene oxide)$_b$-poly(ethylene oxide)$_a$* PEO-PPO-PEO	Oral drug delivery, wound healing	[39]
2.	Temperature	*Gold nanoparticles—Pluronic®F127-Hydroxypropyl methylcellulose* AuNPs-PF127-HPMC	Drug delivery, photothermal platform, skin wound healing	[23]
3.	Temperature	*Poly(oligo(ethylene glycol) methacrylate –co-poly(glycidal methacrylate) copolymers/poly(lactic acid-co-glycolic acid)* P(OEGMA-co-PGMA) copolymers/PLGA	Tissue engineering	[24]
4.	Temperature	*Collagen- or chitosan-based*	Drug delivery	[25]
5.	Temperature	*Poly(N-isopropylacrylamide)- poly(N,N-dimethylacrylamide)- poly(acrylic acid)* PNIPAM-PDMA-PAA	Drug delivery	[26]
6.	Temperature	*Poly(Nisopropylacrylamide-co-sulfobetaine methacrylate) nanogel* PNS nanogels	Diagnosis/chemotherapy	[27]
7.	Electrical	*Poly(3,4-ethylenedioxythiophene)-coated poly(lactic acid-co-glycolic acid) nanofiber* PEDOT-coated PLGA nanofiber	Drug delivery	[28]
8.	Electrical	*Fe_3O_4/Polyaniline* Fe_3O_4/PANI	Antimicrobial, drug delivery	[29]
9.	Electrical	*Polyaniline/gold nanocomposite* PANI/AuNCs	Immunosensor detection of chronic kidney disease	[30]
10.	Electrical	*Polyaniline, poly(3,4-ethylenedioxythiophene)* PANIP, PEDOT	Neural prostheses	[31][32]
11.	Electrochemical	*Biosynthesized gold nanoparticles/ poly(catechol)/graphene sheets/glassy carbon electrode* Bio AuNP/Pol/Gr/GCE	Biosensor, DNA mutation and acute lymphoblastic leukemia detection	[33]
12.	Light	*poly(ethylene glycol)* PEG	Switchable fluorescent probes	[34]
13.	Light	*Ruthenium-containing block copolymer* Poly-Ru nanoparticles	In vivo photodynamic therapy and photochemotherapy	[35]
14.	Magnetic	*Fe_3O_4/methoxy poly(ethylene glycol)-poly-(lactide) composite nanocapsules* Fe_3O_4/MePEG-PLA composite nanocapsules	MRI	[36]
15.	Magnetic	*Trastuzumab (Tra, a humanized monoclonal antibody that specifically recognizes HER2)-doxorubicin poly(vinyl alcohol)/ single-component thiol-functionalized poly (methacrylic acid T-DOX* PVA/PMASH magnetic nanocapsules	Tumor therapy	[37]

Nr. Crt.	Stimuli	Nanomaterial	Application	Reference
16.	Magnetic	*3D collagen hydrogel*	Directed neuronal regeneration	[38]

2.2. Chemical-Responsive Nanomaterials

Examples of chemical-sensitive nanomaterials and their applications are listed in Table 2 [40][41][42][43][44][45][46][47][48][49][50][51]. Recent works [89][90] describe the design of chemical-responsive smart nanomaterials and their applications in the biomedical field.

Table 2. Examples of chemical-responsive nanomaterials and their biomedical applications.

Nr. Crt.	Stimuli	Nanomaterial	Application	Reference.
1.	pH	*Ppoly (ethylene glycol)-Ag nanoparticle* PEG-Ag NPs	Antibacterial, wound healing	[40]
2.	pH	*Hybrid ultra-pH-sensitive (HyUPS) nanotransistor* HyUPS nanotransistors	Receptor-mediated endocytosis in tumor cells	[41]
3.	pH	*Layered double hydroxides-zinc (II) phthalocyanine containing octasulfonate nanohybrid* LDH-ZnPcS8 nanohybrid	Theranostics	[42]
4.	pH	Melanin-like nanoparticles	Photoacoustic imaging of tumors	[43]
5.	pH	*polylactic acid-Resveratrol* PLA-RSV	Drug delivery	[44]
6.	pH	*Poly(carboxybetaine methacrylate)-nanodiamonds* PCBSA-@-NDs	Theranostics	[45]
7.	Redox	*Poly (ethylene glycol)-Pluronic F68-nanoscale covalent organic frameworks* F68@SS-COFs	Cancer therapy	[46]
8.	Redox	*Hyaluronic acid–chitosan–lipoic acid nanoparticles* (HACSLA-NPs)	Breast cancer therapy	[47]
9.	Redox	*Folate redox-responsive chitosan nanoparticles* FTC-NPs	Anticancer drug delivery	[48]
10.	Redox	*Poly (ethylene glycol) conjugated to paclitaxel* via *disulfide linkage* PEG_{2000}-S-S-PTX	Prodrug for breast cancer cells	[49]
11.	Redox	*Prodrug/AgNPs hybrid nanoparticles*	Drug delivery	[50]
12.	Redox	*P[(2-((2- ((camptothecin)-oxy)ethyl)disulfanyl)ethylmethacrylate) -co- (2-(D-galactose)methylmethacryl-ate)] and silver nanoparticles* P(MACPTS-co-MAGP)@AgNPs nanoparticles	Drug release	[51]

2.3. Biological-Responsive Nanomaterials

Examples of biological-sensitive nanomaterials and their applications are listed in Table 3 [52][53][54][55][56][57][58][59][60][61][62]. Recent works describe the design of biological-responsive smart nanomaterials and their applications in the biomedical field.

Table 3. Examples of biological-responsive nanomaterials and their biomedical applications.

Nr. Crt.	Stimuli	Nanomaterial	Application	Reference.
1.	Glucose	*Acetalated dextran nanoparticles* Ac-Dex Nps	Glycemic control	[52]
2.	Glucose	*Boronic acid-derived polymers*	Drug delivery	[53]
3.	Glucose	*Glycidyl methacrylated dextran/Concanavalin A* Dex-GMA/Con A ConA micro/nanospheres	Insulin treatment	[54]

Nr. Crt.	Stimuli	Nanomaterial	Application	Reference.
4.	Glucose	*Chitosan-g-polyethylene glycol monomethyl ether nanocomplex* CS-g-(mPEG) NP	Oral insulin delivery	[55]
5.	Glucose	*Hyaluronic Acid (HA)-coated calcium carbonate NPs*	Oral insulin delivery	[56]
6.	Glucose	Chitosan/poly(gamma-glutamic acid) nanoparticles	Oral insulin delivery	[57]
7.	Glucose	*Carboxymethyl chitosan-phenylboronic acid-Lvaline nanoparticles* (CMCS-PBA-LV) NPs	Oral administration of insulin	[58]
8.	Enzyme	*Nanoplatform formed from Ti substrates modified with layer-by layer mesoporous silica nanoparticles-silver nanoparticles* LBL@MSN-Ag nanoparticles	Tissue growth in vivo and, simultaneously, treat implant-associated bacterial infection	[59]
9.	Enzyme	*Adenosine triphosphate coated with silver nanoparticles* ATP-Ag nanoparticles	Participate in signal transduction and protein activity	[60]
10.	Enzyme	*Activatable low-molecular weight protamine—poly(ethylene glycol) poly(ε-caprolactone) nanoparticles—loaded with paclitaxel* ALMWP-NP-PTX	Glioblastoma therapy	[61]
11.	Enzyme	*Layer-by-layer assembly of poly(2-oxazoline)-based materials*	Therapeutic delivery	[62]

2.4. Dual and Multi-Responsive Nanomaterials

A step forward for biomedical applications is attained when the smart nanomaterials are simultaneously sensitive to more stimuli. The nanomaterials which are sensitive to a few sorts of stimuli are the key for expanding the efficacy of drug delivery and for supporting the diagnosis by monitoring a few physiological changes at once.

The development of nanomaterials with both diagnostic and therapeutic properties is the most powerful technological frontier for moving forward to nanotheranostics. The demand for these technologies is based on the advantage of multiple functions such as multimodal imaging, synergistic therapies, and targeting. The working system of nanotheranostics depends on biological, chemical, and physical triggers considering the activation of the diagnostic and/or the therapeutic properties only at the infected site. In this era of the “war on cancer”, the dual and multi-stimuli-responsive methodology is undeniably appropriate for theranostics as some properties can provide diagnostics, while others could initiate therapy and curing. Consequently, multi-stimuli-sensitive polymers are drawing in expanding consideration for their advantages in the biomedical field.

Multi-stimuli-sensitive polymeric nanoparticles were developed as emerging targeting drug delivery systems. External stimuli such as temperature and pH facilitate the emergence of nanoparticles, while stimuli such as light, the magnetic field, the temperature, and ultrasonic are intended to control drug delivery. Examples of multi-sensitive nanomaterials and their applications are listed in Table 4 [63][64][65][66][67][68][69][70][71][72][73][74][75][76][77].Recent works [143-150] describe the design of multi-responsive smart nanomaterials and their applications in the biomedical field.

Table 4. Examples of dual and multi-responsive nanomaterials and their biomedical applications.

Nr. Crt.	Stimuli	Nanomaterial	Application	Ref.
1.	pH/redox/temperature	*N,N0 -bis(acryloyl)cystamine, Poly(N-isopropylacrylamide), 2-hydroxyethylmethacrylate, Methacrylic acid, a disulfide bond contained cross-linker, and doxorubicin* SS-NPs@DOX	Drug delivery	[63]
2.	Ultrasound/pH	*Poly(ethylene oxide, 2-(diethylamino)ethyl methacrylate, (2-tetrahydrofuranyloxy)ethyl methacrylate* PEO43-b-P(DEA33-stat-TMA	Drug release	[64]

Nr. Crt.	Stimuli	Nanomaterial	Application	Ref.
3.	Temperature/magnetic field	*Poly(N-isopropylacrylamide)- Magnetic nanoparticles* b-PNIPAM-mNPs	The isolation of diagnostic targets that can be used in point-of-care devices	[65]
4.	Light/pH	rGO-PDA nanosheets	Drug delivery, phototherapy	[66]
5.	pH/magnetic field	*Magnetic nanoparticles* MFNPs	Targeting, drug delivery, MRI	[67]
6.	Temperature/pH	*Poly(N-isopropylacrylamide)* pNIPAM	Drug release	[68]
7.	pH/light/enzyme	*Copper sulfide nanoparticles* CuS NPs	Theranostics	[69]
8.	pH/redox	*Thiol-modified polylysine- indocyanine green/ poly(ethylene glycol) nanoparticles* PLL-ICG/DPEG Nps	Photothermal and photodynamic therapy	[70]
9.	pH/redox	*Poly (ethylene glycol) –polylacticacid-thioketal groups-Paclitaxel-(Maleimide thioether) Chlorin e6* mPEG-PLA-TKI-PTX nanoparticles and Ce6-(SS-mal-)-Ce6 (PNPCe6)	Chemotherapy, drug release	[71]
10.	pH/redox	*Histidine -4 polyamidoamine dendrimer -Disulfide bonds- (poly (ethylene glycol)- Transferrin* (His-PAMAM-ss-PEG-Tf, HP-ss-PEG-Tf) nanocarrier	Anticancer drug delivery	[72]
11.	pH/redox	*Lipoic acid ethylenediamine- Polyethylene glycol diglycidyl ether- L-lysine* poly(LAE-co-PGDE-co-Lys) core-crosslinked nano aggregate	Anticancer drug delivery	[73]
12.	pH/redox	*Paclitaxel- poly(6-O-methacryloyl-d-galactopyranose)-gemcitabine/ N-acetyl-d-glucosamine(NAG)-poly(styrene-alt-maleic anhydride)-b-polystyrene* PTXL-ss-PMAGP-GEM/NAG NLCs	Anticancer drug delivery	[74]
13.	UV light/redox/pH	*Six-arm star-shaped amphiphilic copolymer with poly (caprolactone) -bpoly (acrylic acid) -b-poly (poly (ethylene glycol) methyl ether methacrylate)*	Anticancer drug delivery	[75]
14.	pH/temperature	Poly(NIPAM)nanogel @ Fe_3O_4 NPs/poly(acrylic acid) -graft—κ—carrageenan	Drug delivery	[76]
15.	Redox/pH/temperature	*Nanogels based on alginate and cystamine*	Anticancer drug delivery	[77]

3. Advances in Plasmonic Nanomaterials

A special class of smart nanomaterials is derived from plasmonic nanoparticles used in innovative sensitive tools for diagnostics and therapeutics. The collective electronic (plasmon) resonances of noble/coinage metal nanoparticles enable a strong optical response essential in applications such as photocatalysis, sensing, photothermal heating, and enhanced fluorescence. Biomedical applications rely on plasmonic nanoparticles' properties to absorb or scatter light at near-infrared wavelengths, transmissive in the human body [78]. A large number of applications misuse the extraordinary properties of metals to support electromagnetic waves at their surfaces, through the oscillation of their conduction electrons known as surface plasmons. The local dielectric environment, size, structure, shape, and composition determine the surface plasmon polariton modes enabling nanostructures to focus and direct light down to the nanoscale. The ability of plasmonic nanostructures to strongly interact with light at wavelengths that significantly exceed their dimensions led to the appearance of the nanoplasmoic field [79]. Consequently, most recent strategies for the design and manufacture of plasmonic nanostructures for accurately controlling light have opened new entryways for the applications that were recently perceived as impossible.

Recent studies have shown that by targeting gold nanoparticles to the cell nucleus region, the nuclear stiffness is enhanced, slowing down the migration and invasion speed of cancer cells and suppressing metastasis [80]. Further, gold nanoparticles exhibit high contrast in photothermal therapeutic treatments, as well as photoacoustic, optical coherence, and X-ray CT imaging. Conjugates of gold nanoparticles present augmented binding affinity, long circulatory half-life, size-

enhanced tumor uptake, increased targeting selectivity, high biocompatibility, and rapid transport kinetics. If all those properties are put together in a highly multifunctional platform, one can obtain an increasingly selective and potent oncologic treatment [81].

As diagnosis is the key in the screening and treatment of human diseases, modern-day researchers developed sensitive tools for real-time and accurate tracking of the treatment effect. In a recent paper, the authors obtained a core–shell structure MPs@ SiO2@Pd–Au with a crystalline magnetic core, amorphous silica interaction layer, and Pd–Au shell for medulloblastoma diagnosis and radiotherapy evaluation. Owing to the plasmonic and alloying effects, MPs@SiO2@Pd–Au may contribute to efficient electron transfer and high surface stability under laser irradiation during the laser desorption/ionization process [82]. Other authors described the design of a plasmonic gold nano-island (pGold) chip assay for enhanced diagnosis and monitoring of myocardial infarction [83]. A multifunctional platinum nanoreactor intended for point-of-care metabolic analysis, visual detection, and mass spectrometry fingerprinting for in vitro pancreatic cancer diagnostics was designed using controlled core–shell structured Fe3O4@SiO2@Pt particles [84]. Another work describing the application of laser desorption/ionization mass spectrometry in large-scale clinical in vitro cervical cancer diagnosis utilized a plasmonic chip with Au nanoparticles deposited on a dopamine bubble layer [85].

An increasing interest was paid to the field of thermoplasmonics, defined as plasmonic nanoparticles remotely controlled by light to release heat on the nanoscale volumes. The capability of using plasmonic materials as photothermal agents is based on a combination of properties such as the high density of free electrons, the absence of thermobleaching, resonances that enhance light–matter interaction, and low losses for noble metals. Those materials are best choices in applications requiring spatially confined heating, such as in nanosurgery and photoacoustic and photothermal imaging [86]. Recent works described the capability of gold nanorods to convert NIR radiation into heat for antibacterial application without affecting cells' viability and proliferation [87] and of keratin-coated gold nanoparticles to kill the brain cancer cells by photothermal therapy [88]. The photothermal therapy induced by the presence of gold nanoparticles in a system capable to develop immunotherapy represents a major breakthrough in the fight against malignant solid tumors. This synergistic new approach was comprehensively described moving from in vivo studies to clinical trial applications in patients suffering from solid tumors. Although those systems hold great promise in nanomedicine, there are still risks involved, such as the wrong cells being targeted, unknown long-term side effects, and unwanted immune reaction systems. For this reason, the combination of hyperthermia with chemotherapeutic activity or cancer immunotherapy demonstrated improved care of oncological patients [89].

The properties of Au and Ag nanoparticles have inspired the field of plasmonic nanoparticles in the last two decades, but recently, non-noble metals have been the subject of quickly expanding interest as less expensive, more practical alternatives. Colloidal nanocrystals functionalized with silica have been utilized for plasmon-driven photocatalysis and surface-enhanced Raman spectroscopy at visible and near-infrared wavelengths due to their enhanced stability in water and efficient broadband photothermal heating [90].

References

1. Amador-Vargas, S.; Dominguez, M.; León, G.; Maldonado, B.; Murillo, J.; Vides, G.L. Leaf-folding response of a sensitive plant shows context-dependent behavioral plasticity. Plant Ecol. 2014, 215, 1445–1454.
2. Reyssat, E.; Mahadevan, L. Hygromorphs: From pine cones to biomimetic bilayers. J. R. Soc. Interface 2009, 6, 951–957.
3. Elbaum, R.; Zaltzman, L.; Burgert, I.; Fratzl, P. The role of wheat awns in the seed dispersal unit. Science 2007, 316, 884–886.
4. Erb, R.M.; Sander, J.S.; Grisch, R.; Studart, A.R. Self-shaping composites with programmable bioinspired microstructures. Nat. Commun. 2013, 4, 1712.
5. Forterre, Y.; Skotheim, J.M.; Dumais, J.; Mahadevan, L. How the Venus flytrap snaps. Nature 2005, 433, 421–425.
6. Fu, Q.; Li, C. Robotic modelling of snake traversing large, smooth obstacles reveals stability benefits of body compliance. R. Soc. Open Sci. 2020, 7, 191192.
7. Teyssier, J.; Saenko, S.V.; Van Der Marel, D.; Milinkovitch, M.C. Photonic crystals cause active colour change in chameleons. Nat. Commun. 2015, 6, 6368.
8. Totakagi, T. A Concept of intelligent materials. J. Intell. Mater. Syst. Struct. 1990, 1, 149–156.
9. Totakagi, T. Proceedings of the International Workshop on Intelligent Materials, Tsukuba Science City; The Society of Non-Traditional Technology: Tokyo, Japan, 1989.

10. Feynman, R. There’s plenty of room at the bottom. Eng. Sci. 1960, 23, 22–36.
11. Taniguchi, N. On the basic concept of ‘nano-technology’. In International Conference on Production Engineering, Part II; Japan Society of Precision Engineering: Tokyo, Japan, 1974.
12. Roco, M.C. International strategy for nanotechnology research and development. J. Nanoparticle Res. 2001, 3, 353–360.
13. Aflori, M.; Butnaru, M.; Tihauan, B.-M.; Doroftei, F. Eco-friendly method for tailoring biocompatible and antimicrobial surfaces of poly-L-lactic acid. Nanomaterials 2019, 9, 428.
14. Genchi, G.G.; Marino, A.; Tapeinos, C.; Ciofani, G. Smart materials meet multifunctional biomedical devices: Current and prospective implications for nanomedicine. Front. Bioeng. Biotechnol. 2017, 5, 80.
15. Cabane, E.; Zhang, X.; Langowska, K.; Palivan, C.G.; Meier, W. Stimuli-responsive polymers and their applications in nano-medicine. Biointerphases 2012, 7, 9.
16. Thangudu, S. Next generation nanomaterials: Smart nanomaterials, significance, and biomedical applications. In Applications of Nanomaterials in Human Health; Khan, F.A., Ed.; Springer: Singapore, 2020; pp. 287–312.
17. Pinteala, M.; Abadie, M.J.M.; Rusu, R.D. Smart supra-and macro-molecular tools for biomedical applications. Materials 2020, 13, 3343.
18. Das, S.S.; Bharadwaj, P.; Bilal, M.; Barani, M.; Rahdar, A.; Taboada, P.; Bungau, S.; Kyzas, G.Z. Stimuli-responsive polymeric nanocarriers for drug delivery, imaging, and theragnosis. Polymers 2020, 12, 1397.
19. Aflori, M. (Ed.) Intelligent Polymers for Nanomedicine and Biotechnologies; CRC Press: Boca Raton, FL, USA, 2017.
20. Flory, P.J. Thermodynamics of high polymer solutions. J. Chem. Phys. 1941, 9, 660.
21. Huggins, M.L. Some properties of solutions of long-chain compounds. J. Phys. Chem. 1942, 46, 151–158.
22. Aguilar, M.R.; San Roman, J. Introduction to smart polymers and their applications. In Smart Polymers and their Applications; Woodhead Publish: Cambridge, UK, 2014; Volume 1, pp. 1–11.
23. Arafa, M.G.; El-Kased, R.F.; Elmazar, M.M. Thermoresponsive gels containing gold nanoparticles as smart antibacterial and wound healing agents. Sci. Rep. 2018, 8, 1–16.
24. Debashish, R.W.L.; Brooks, A.; Sumerlin, B.S. New directions in thermoresponsive polymers. Chem. Soc. Rev. 2013, 42, 7214–7243.
25. Hoffman, A.S. Stimuli-responsive polymers: Biomedical applications and challenges for clinical translation. Adv. Drug Deliv. Rev. 2013, 65, 10–16.
26. Chen, Y.; Gao, Y.; Da Silva, L.P.; Pirraco, R.P.; Ma, M.; Yang, L.; Reis, R.L.; Chen, J. A thermo-/pH-responsive hydrogel (PNIPAM-PDMA-PAA) with diverse nanostructures and gel behaviors as a general drug carrier for drug release. Polym. Chem. 2018, 9, 4063–4072.
27. Zheng, A.; Wu, D.; Fan, M.; Wang, H.; Liao, Y.; Wang, Q.; Yang, Y. Injectable zwitterionic thermosensitive hydrogels with low-protein adsorption and combined effect of photothermal-chemotherapy. J. Mater. Chem. B 2020, 8, 10637–10649.
28. Abidian, M.R.; Kim, D.-H.; Martin, D.C. Conducting-polymer nanotubes for controlled drug. Adv. Mater. 2006, 18, 405–409.
29. Hossain, M.K.; Minami, H.; Hoque, S.M.; Rahman, M.M.; Sharafat, M.K.; Begum, M.F.; Islam, M.E.; Ahmad, H. Mesoporous electromagnetic composite particles: Electric current responsive release of biologically active molecules and antibacterial properties. Colloids Surf. B 2019, 181, 85–93.
30. Shaikh, M.O.; Srikanth, B.; Zhu, P.-Y.; Chuang, C.-H. Impedimetric immunosensor utilizing polyaniline/Gold nanocomposite-modified screen-printed electrodes for early detection of chronic kidney disease. Sensors 2019, 19, 3990.
31. Otto, K.J.; Schmidt, C.E. Neuron-targeted electrical modulation. Science 2020, 367, 1303–1304.
32. Liu, J.; Kim, Y.S.; Joubert, L.-M.; Jiang, Y.; Wang, H.; Fenno, L.E.; Tok, J.B.-H.; Paşca, S.P.; Shen, K.; Bao, Z.; et al. Genetically targeted chemical assembly of functional materials in living cells, tissues, and animals. Science 2020, 367, 1372–1376.
33. Mazloum-Ardakani, M.; Barazesh, B.; Khoshroo, A.; Moshtaghiun, M.; Sheikhha, M.H. A new composite consisting of electro-synthesized conducting polymers, graphene sheets and biosynthesized gold nanoparticles for biosensing acute lymphoblastic leukemia. Bioelectrochemistry 2018, 121, 38–45.
34. Klajn, R. Spiropyran-based dynamic materials. Chem. Soc. Rev. 2014, 43, 148–184.

35. Sun, W.; Li, S.; Haupler, B.; Liu, J.; Jin, S.; Steffen, W.; Schubert, U.S.; Butt, H.-J.; Liang, X.-J.; Wu, S. An amphiphilic ruthenium polymetallodrug for combined photodynamic therapy and potochemotherapy in vivo. Adv. Mater. 2017, 29, 1603702.

36. Xu, B.; Dou, H.; Tao, K.; Sun, K.; Ding, J.; Shi, W.; Guo, X.; Li, J.; Zhang, D.; Sun, K. Two-in-one fabrication of Fe3O4/MePEG-PLA composite nanocapsules as a potential ultrasonic/MRI dual contrast agent. Langmuir 2011, 27, 12134–12142.

37. Chiang, C.; Shen, Y.-S.; Liu, J.-J.; Shyu, W.-C.; Chen, S.-Y. Synergistic combination of multistage magnetic guidance and optimized ligand density in targeting a nanoplatform for enhanced cancer therapy. Adv. Health Mater. 2016, 5, 2131–2141.

38. Antman-Passig, M.; Shefi, O. Remote magnetic orientation of 3D collagen hydrogels for directed neuronal regeneration. Nano Lett. 2016, 16, 2567–2573.

39. Liu, Y.; Yang, F.; Feng, L.; Yang, L.; Chen, L.; Wei, G.; Lu, W. In vivo retention of poloxamer based in situ hydrogels for vaginal application in mouse and rat models. Acta Pharm. Sin. B 2017, 7, 502–509.

40. Xie, X.; Sun, T.C.; Xue, J.; Miao, Z.; Yan, X.; Fang, W.; Li, Q.; Tang, R.; Lu, Y.; Tang, L.; et al. AG nanoparticles cluster with PH-triggered reassembly in targeting antimicrobial applications. Adv. Funct. Mater. 2020, 30, 2000511.

41. Wang, Y.; Wang, C.; Li, Y.; Huang, G.; Zhao, T.; Ma, X.; Wang, Z.; Sumer, B.D.; White, M.A.; Gao, J. Digitization of endocytic PH by hybrid ultra-PH-sensitive nanoprobes at single-organelle resolution. Adv. Mater. 2017, 29.

42. Li, X.; Zheng, B.-Y.; Ke, M.-R.; Zhang, Y.; Huang, J.-D.; Yoon, J. A tumor-pH-responsive supramolecular photosensitizer for Activatable photodynamic therapy with minimal in vivo skin Phototoxicity. Theranostics 2017, 7, 2746–2756.

43. Ju, K.-Y.; Kang, J.; Pyo, J.; Lim, J.; Chang, J.H.; Lee, J.-K. pH-induced aggregated melanin nanoparticles for photoacoustic signal amplification. Nanoscale 2016, 8, 14448–14456.

44. Bonadies, I.; Di Cristo, F.; Peluso, A.V.G.; Calarco, A.; Salle, A.D. Resveratrol-loaded electrospun membranes for the prevention of implant-associated infections. Nanomaterials 2020, 10, 1175.

45. Zhou, B.; Li, J.; Lu, B.; Wu, W.; Zhang, L.; Liang, J.; Yi, J.; Li, X. Novel polyzwitterion shell with adaptable surface chemistry engineered to enhance anti-fouling and intracellular imaging of detonation nanodiamonds under tumor pHe. Front. Mater. Sci. 2020, 14, 402–412.

46. Liu, S.; Yang, J.; Guo, R.; Deng, L.; Dong, A.; Zhang, J. Facile fabrication of redox-responsive covalent organic framework nanocarriers for efficiently loading and delivering doxorubicin. Macromol. Rapid Commun. 2020, 41, e1900570.

47. Rezaei, S.; Kashanian, S.; Bahrami, Y.; Cruz, L.J.; Motiei, M. Redox-sensitive and hyaluronic acid-functionalized nanoparticles for improving breast cancer treatment by cytoplasmic 17α-methyltestosterone delivery. Molecules 2020, 25, 1181.

48. Mazzotta, E.; De Benedittis, S.; Qualtieri, A.; Muzzalupo, R. Actively targeted and redox responsive delivery of anticancer drug by chitosan nanoparticles. Pharmaceutics 2019, 12, 26.

49. Mutlu-Agardan, N.B.; Sarisozen, C.; Torchilin, V.P. Cytotoxicity of novel redox sensitive PEG2000-S-S-PTX micelles against drug-resistant ovarian and breast cancer cells. Pharm. Res. 2020, 37, 1–8.

50. Mollazadeh, S.; Mackiewicz, M.; Yazdimamaghani, M. Recent advances in the redox-responsive drug delivery nanoplatforms: A chemical structure and physical property perspective. Mater. Sci. Eng. C 2021, 118, 111536.

51. Qiu, L.; Zhao, L.; Xing, C.; Zhan, Y. Redox-responsive polymer prodrug/AgNPs hybrid nanoparticles for drug delivery. Chin. Chem. Lett. 2018, 29, 301–304.

52. Volpatti, L.R.; Matranga, M.A.; Cortinas, A.B.; Delcassian, D.; Daniel, K.B.; Langer, R.; Anderson, D.G. Glucose-responsive nanoparticles for rapid and extended self-regulated insulin delivery. ACS Nano 2019, 14, 488–497.

53. Tang, W.; Chen, C. Hydrogel-based colloidal photonic crystal devices for glucose sensing. Polymers 2020, 12, 625.

54. Yin, R.; He, J.; Bai, M.; Huang, C.; Wang, K.; Zhang, H.; Yang, S.-M.; Zhang, W.; Yang, S.-M. Engineering synthetic artificial pancreas using chitosan hydrogels integrated with glucose-responsive microspheres for insulin delivery. Mater. Sci. Eng. C 2019, 96, 374–382.

55. Liu, C.; Kou, Y.; Zhang, X.; Dong, W.; Cheng, H.; Mao, S. Enhanced oral insulin delivery via surface hydrophilic modification of chitosan copolymer based self-assembly polyelectrolyte nanocomplex. Int. J. Pharm. 2019, 554, 36–47.

56. Liu, D.; Jiang, G.; Yu, W.; Li, L.; Tong, Z.; Kong, X.; Yao, J. Oral delivery of insulin using CaCO3-based composite nanocarriers with hyaluronic acid coatings. Mater. Lett. 2017, 188, 263–266.

57. Sonaje, K.; Chen, Y.J.; Chen, H.L.; Wey, S.-P.; Juang, J.-H.; Nguyen, H.-N.; Hsu, C.-W.; Lin, K.J.; Sung, H.W. Enteric-coated capsules filled with freeze-dried chitosan/poly(g-glutamic acid) nanoparticles for oral insulin delivery.

Biomaterials 2010, 31, 3384–3394.

58. Li, L.; Jiang, G.; Yu, W.; Liu, D.; Chen, H.; Liu, Y.; Tong, Z.; Kong, X.; Yao, J. Preparation of chitosan-based multifunctional nanocarriers overcoming multiple barriers for oral delivery of insulin. Mater. Sci. Eng. C 2017, 70, 278–286.
59. Ding, Y.; Hao, Y.; Yuan, Z.; Tao, B.; Chen, M.; Lin, C.; Liu, P.; Caib, K. A dual-functional implant with an enzyme-responsive effect for bacterial infection therapy and tissue regeneration. Biomater. Sci. 2020, 8, 1840–1854.
60. Datta, L.P.; Chatterjee, A.; Acharya, K.; De, P.; Das, M. Enzyme responsive nucleotide functionalized silver nanoparticles with effective antimicrobial and anticancer activity. New J. Chem. 2017, 41, 1538–1548.
61. Gu, G.; Xia, H.; Hu, Q.; Liu, Z.; Jiang, M.; Kang, T.; Miao, D.; Tu, Y.; Pang, Z.; Song, Q.; et al. PEG-co-PCL nanoparticles modified with MMP-2/9 activatable low molecular weight protamine for enhanced targeted glioblastoma therapy. Biomaterials 2013, 34, 196–208.
62. Gunawan, S.T.; Kempe, K.; Hagemeyer, C.E.; Caruso, F.; Bonnard, T.; Cui, J.; Alt, K.; Law, L.S.; Wang, X.; Westein, E.; et al. Multifunctional thrombin-activatable polymer capsules for specific targeting to activated platelets. Adv. Mater. 2015, 27, 5153–5157.
63. Yu, B.; Song, N.; Hu, H.; Chen, G.; Shen, Y.; Cong, H. A degradable triple temperature-, pH-, and redox-responsive drug system for cancer chemotherapy. J. Biomed. Mater. Res. Part A 2018, 106, 3203–3210.
64. Chen, W.; Du, J. Ultrasound and PH dually responsive polymer vesicles for anticancer drug delivery. Sci. Rep. 2013, 3, srep02162.
65. Lai, J.J.; Hoffman, J.M.; Ebara, M.; Hoffman, A.S.; Estournès, C.; Wattiaux, A.; Stayton, P.S. Dual magnetic-/Temperature-responsive nanoparticles for microfluidic separations and assays. Langmuir 2007, 23, 7385–7391.
66. Jiang, W.; Mo, F.; Lin, Y.; Wang, X.; Xu, L.; Fu, F. 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 2018, 6, 4360–4367.
67. Bhattacharya, D.; Behera, B.; Sahu, S.K.; Ananthakrishnan, R.; Maiti, T.K.; Pramanik, P. Design of dual stimuli responsive polymer modified magnetic nanoparticles for targeted anti-cancer drug delivery and enhanced MR imaging. New J. Chem. 2015, 40, 545–557.
68. Chen, Y.; Wei, W.; Zhu, Y.; Luo, J.; Liu, R.; Liu, X. Synthesis of temperature/PH dual-stimuli-response multicompartmental microcapsules via pickering emulsion for preprogrammable payload release. ACS Appl. Mater. Interfaces 2020, 12, 4821–4832.
69. Poudel, K.; Gautam, M.; Jin, S.G.; Choi, H.-G.; Yong, C.S.; Kim, J.O. Copper sulfide: An emerging adaptable nanoplatform in cancer theranostics. Int. J. Pharm. 2019, 562, 135–150.
70. Zhang, P.; Gao, Z.; Cui, J.; Hao, J. Dual-stimuli-responsive polypeptide nanoparticles for photothermal and photodynamic therapy. ACS Appl. Bio Mater. 2020, 3, 561–569.
71. Lu, H.; Zhao, Q.; Wang, X.; Mao, Y.; Chen, C.; Gao, Y.; Sun, C.; Wang, S. Multi-stimuli responsive mesoporous silica-coated carbon nanoparticles for chemo-photothermal therapy of tumor. Colloids Surf. B 2020, 190, 110941.
72. Shi, Y.; Shan, S.; Li, C.; Song, X.; Zhang, C.; Chen, J.; You, J.; Xiong, J. Application of the tumor site recognizable and dual-responsive nanoparticles for combinational treatment of the drug-resistant colorectal cancer. Pharm. Res. 2020, 37, 1–14.
73. Hu, Q.; Wang, Y.; Xu, L.; Chen, D.; Cheng, L. Transferrin conjugated PH- and redox-responsive poly(Amidoamine) Dendrimer conjugate as an efficient drug delivery carrier for cancer therapy. Int. J. Nanomed. 2020, 15, 2751–2764.
74. Liang, Y.; Zhang, J.; Tian, B.; Wu, Z.; Svirskis, D.; Han, J. A NAG-guided nano-delivery system for redox-and pH-triggered intracellularly sequential drug release in cancer cells. Int. J. Nanomed. 2020, 15, 841.
75. Huang, Y.; Tang, Z.; Peng, S.; Zhang, J.; Wang, W.; Wang, Q.; Lin, W.; Lin, X.; Zu, X.; Luo, H.; et al. pH/redox/UV irradiation multi-stimuli responsive nanogels from star copolymer micelles and Fe3+ complexation for “on-demand” anticancer drug delivery. React. Funct. Polym. 2020, 149, 104532.
76. Bardajee, G.R.; Khamooshi, N.; Nasri, S.; Vancaeyzeele, C. Multi-stimuli responsive nanogel/hydrogel nanocomposites based on κ-carrageenan for prolonged release of levodopa as model drug. Int. J. Biol. Macromol. 2020, 153, 180–189.
77. Xu, X.; Wang, X.; Luo, W.; Qian, Q.; Li, Q.; Han, B.; Liu, C. Triple cell-responsive nanogels for delivery of drug into cancer cells. Colloids Surf. B 2018, 163, 362–368.
78. Halas, N.J. Connecting the dots: Reinventing optics for nanoscale dimensions. Proc. Natl. Acad. Sci. USA 2009, 106, 3643–3644.

79. Lal, S.; Clare, S.E.; Halas, N.J. Nanoshell-enabled photothermal cancer therapy: Impending clinical impact. Accounts Chem. Res. 2008, 41, 1842–1851.
80. Ali, M.R.K.; Wu, Y.; Ghosh, D.; Do, B.H.; Chen, K.; Dawson, M.R.; Fang, N.; Sulchek, T.A.; El-Sayed, M.A. Nuclear membrane-targeted gold nanoparticles inhibit cancer cell migration and invasion. ACS Nano 2017, 11, 3716–3726.
81. Dreaden, E.C.; Mackey, M.A.; Huang, X.; Kangy, B.; El-Sayed, M.A. Beating cancer in multiple ways using nanogold. Chem. Soc. Rev. 2011, 40, 3391–3404.
82. Cao, J.; Shi, X.; Gurav, D.D.; Huang, L.; Su, H.; Li, K.; Niu, J.; Zhang, M.; Wang, Q.; Jiang, M.; et al. Metabolic fingerprinting on synthetic alloys for medulloblastoma diagnosis and radiotherapy evaluation. Adv. Mater. 2020, 32, 2000906.
83. Xu, W.; Wang, L.; Dai, H.; Sun, X.; Huang, L.; Su, H.; Wei, X.; Chen, C.-C.; Lou, J.; Dai, H.; et al. Diagnosis and prognosis of myocardial infarction on a plasmonic chip. Nat. Commun. 2020, 11, 1–9.
84. Huang, L.; Gurav, D.D.; Price, C.-A.H.; Velliou, E.; Liu, J.; Qian, K.; Wu, S.; Xu, W.; Vedarethinam, V.; Yang, J.; et al. A multifunctional platinum nanoreactor for point-of-care metabolic analysis. Matter 2019, 1, 1669–1680.
85. Shu, W.; Wang, Y.; Liu, C.; Li, R.; Pei, C.; Lou, W.; Lin, S.; Di, W.; Wan, J. Construction of a plasmonic chip for metabolic analysis in cervical cancer screening and evaluation. Small Methods 2019, 4, 190046.
86. Baffou, G.; Cichos, F.; Quidant, R. Applications and challenges of thermoplasmonics. Nat. Mater. 2020, 19, 946–958.
87. Annesi, F.; Pane, A.; Bartolino, R.; De Sio, L.; Losso, M.A.; Guglielmelli, A.; Lucente, F.; Petronella, F.; Placido, T.; Comparelli, R.; et al. Thermo-plasmonic killing of Escherichia coli tg1 bacteria. Materials 2019, 12, 1530.
88. Guglielmelli, A.; Rosa, P.; Perotto, G.; De Sio, L.; Contardi, M.; Prato, M.; Mangino, G.; Miglietta, S.; Petrozza, V.; Pani, R.; et al. Biomimetic keratin gold nanoparticle-mediated in vitro photothermal therapy on glioblastoma multiforme. Nanomedicine 2021, 4.
89. De Angelis, B.; DePalo, N.; Petronella, F.; Quintarelli, C.; Curri, M.L.; Pani, R.; Calogero, A.; Locatelli, F.; De Sio, L. Stimuli-responsive nanoparticle-assisted immunotherapy: A new weapon against solid tumours. J. Mater. Chem. B 2020, 8, 1823–1840.
90. Renard, D.; Tian, S.; Lou, M.; Neumann, O.; Yang, J.; Bayles, A.; Solti, D.; Nordlander, P.; Halas, N.J. Uv-resonant al nanocrystals: Synthesis, silica coating, and broadband photothermal response. Nano Lett. 2020, 21.
