Review

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Polymer-Based Nanomaterials for Photothermal Therapy: From Light-Responsive to Multifunctional Nanoplatforms for Synergistically Combined Technologies

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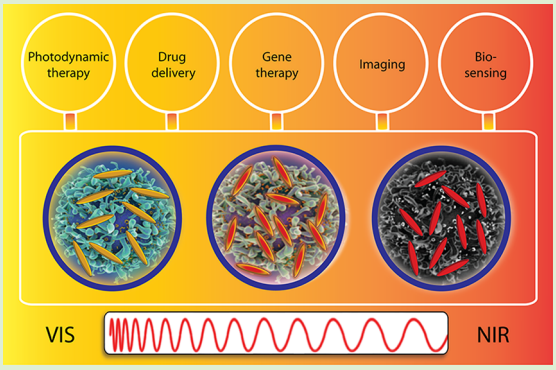
ABSTRACT: Materials for the treatment of cancer have been studied comprehensively over the past few decades. Among the various kinds of biomaterials, polymer-based nanomaterials represent one of the most interesting research directions in nanomedicine because their controlled synthesis and tailored designs make it possible to obtain nanostructures with biomimetic features and outstanding biocompatibility. Understanding the chemical and physical mechanisms behind the cascading stimuli-responsiveness of *smart* polymers is fundamental for the design of multifunctional nanomaterials to be used as photothermal agents for targeted polytherapy. In this review, we offer an in-depth overview of the recent advances in polymer nanomaterials for photothermal therapy, describing the features of three different types of polymer-based nanomaterials. In each case, we systematically show the relevant benefits, highlighting the strategies for developing light-controlled multifunctional nanoplatforms that are responsive in a cascade manner and addressing the open issues by means of an inclusive state-of-the-art review. Moreover, we face further challenges and provide new perspectives for future strategies for developing novel polymeric nanomaterials for photothermally assisted therapies.



1. INTRODUCTION

Cancer is a class of more than one hundred diseases involving out-of-control growth of abnormal cells in the human body.[1] The number of people suffering from cancer is dramatically high. The World Health Organization (WHO) estimates that cancer is the second leading cause of death worldwide, and that it was responsible for 8.8 million deaths in 2015.[2] Moreover, it accounted for ∼16% of all the world's deaths in 2015, and it is expected to continue rising. The estimated annual worldwide cost of cancer to society, 1.16 trillion US dollars, highlights the enormous impact that it has on global socioeconomic conditions.[3]

Cancer has been recognized as a serious disease since ancient times. Hippocrates, the father of medicine, classified and studied several kinds of cancer more than 2,000 years ago. During his studies, he investigated different types of treatment, including the cauterization of surface tumors by using a hot metal, concluding in the end that "if a tumor cannot be cut, it should be burned. If it cannot be burned, then it is incurable".[4]

The theory that cancer may be cured by artificially controlling body temperature has been evaluated scrupulously over the last few decades. Many studies underlined the fact that normal and cancer cells have different responses to heat and that temperatures over 42.5 °C are actually cytotoxic for tumor cells.[5] This concept paved the way to a new treatment called hyperthermia therapy.[6] Conventional hyperthermia systems are designed to heat tissue to ∼42.5−44.0 °C to stimulate the immune system response for the nonspecific immunotherapy of cancers and to induce the regression or complete disappearance of the cancer by direct cell damage.[7] Unfortunately, in clinical conditions the use of hyperthermia as a stand-alone treatment of cancer has been proven ineffective.[8] High temperatures can eliminate a large number of tumor cells, but it is difficult to heat the local tumor region without causing damage to the surrounding tissues. Hyperthermia exhibits several technical problems mainly related to the heating of relevant portions of the human body and to the serious side effects caused to patients.[9] Lastly, this technique is only applied as an additional therapy in combination with conventional cancer treatments (e.g., chemotherapy and radiotherapy).[8]

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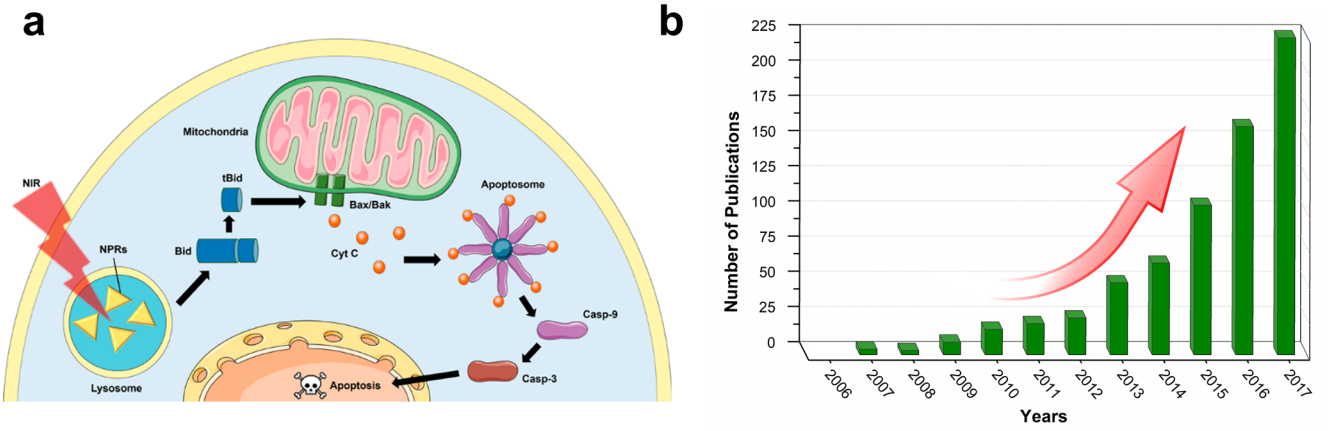

Figure 1. (a) Scheme illustrating the biochemical mechanism resulting from nanomaterial-mediated photothermal therapy. Reprinted with permission from ref 10. Copyright 2015, American Chemical Society. (b) Number of published articles on polymer-based nanomaterials for photothermal therapy during the period 2006−2017 obtained from the Web of Science database.

The development of effective tumor treatments is one of the greatest challenges in healthcare today. Therefore, huge investments have been made in research with a view to developing new treatments or improving the already existing ones. Scrupulous attention has recently been focused on the application of heat in cancer treatments with the possibility to "burn" a tumor at the cellular level, thus reducing the main drawbacks of conventional hyperthermia. The key to the efficient and successful treatment of a tumor using heat is the development of a noninvasive therapy that leads to the local treatment of cancer cells only.[10]

Photothermal therapy (PTT) is a newly developed and promising therapeutic strategy which is considered the natural evolution of conventional hyperthermia therapy, because it uses agents capable of physically reaching specific cancer cells and generating heat because of the interaction with light.[11] PTT involves the use of nanometer-sized materials that show high absorption in the near-infrared (NIR) region.[12] This biological tissue-transparent radiation can penetrate living tissues without causing damage. The light absorbed by these nanomaterials is rapidly converted into heat, causing tumor cell apoptosis (Figure 1a) and avoiding the typical drawbacks of hyperthermia.[10]

The development of future medical technologies capable of enhancing therapeutic efficiency and reducing their side effects will mainly be the result of the enormous scientific effort put into material science, which has led to the rapid development of nanotechnology.[13] Today, the rapid expansion of this field has led to a generation of biomaterials with fascinating properties and activities.[14] Unfortunately, the first generations of biomaterials already applied were designed without fully taking into consideration the fast and significant changes that occur in biological tissues. The possibility of using external stimuli to trigger changes in biomaterial properties affords a high level of control over the activities of implanted material over time, which is necessary for developing a new generation of biomedical materials.[15] One of the main goals of nanomaterial sciences for biomedical application is that of developing biocompatible materials in which changes in properties and activities are triggered through artificial stimuli, such as light irradiation,[16] magnetic,[17] pH,[18] thermal,[19] and electrical stimulations.[20]

The complex functions of living systems are mainly driven by regulation systems that provide feedback to stabilize such extremely dynamic and nonequilibrium systems.[21] Nature uses different kinds of approaches to perform life processes precisely based on response cascades.[22] Nature has been a source of inspiration for scientists in the development of new technologies and materials because it offers a wide range of multifunctional materials capable of responding to stimuli in a controlled way.[23] In the past decades, biomimetic approaches have been used by scientists to develop stimuli-responsive materials that try to mimic nature.[24] Sensitive materials that respond to small environmental condition changes with dramatic material property variations are known as *stimuli-responsive*, *smart*, or *intelligent* materials. Smart nanomaterials can be classified according to the stimuli they are sensitive to (e.g., temperature, pH, ionic strength, light, electric or magnetic field).[25] Moreover, some of these materials can respond to a combination of different kinds of stimuli.[26] Stimuli-responsive materials became essential in the area of biomedical applications to develop brand new diagnostic and therapeutic techniques, and especially nanomaterials, because nanotechnology shows remarkable potential in this field.[27]

Nanomedicine is an extremely dynamic field and PTT, due to its noninvasive character for the selective treatment of tumors, is one of its most studied branches. Several scientific articles published by different research groups have proven the possibility of synthesizing nanomaterials with interesting optical properties in the near-infrared region, such as the fast and efficient light-to-heat conversion that can be delivered to specific tissues. The unique optical properties of nanomaterials confirm the potential for the creation of new functional materials for photothermal cancer therapy.[28] Recently, several kinds of nanomaterials that are good absorbers of NIR radiation have been developed. The first and most widely studied group of materials is composed of noble metal nanomaterials (e.g., gold and silver nanoparticles).[29] The surface plasmon resonance, a phenomenon that leads to the collective excitation of electrons in these metal nanostructures, has been widely examined to strongly enhance the material's optical response, such as the NIR radiation absorption, scattering, and conversion.[30] Despite the huge efforts of the scientific community to improve metal nanomaterials for PTT, the accumulation of such metallic nanoparticles in the body and their potential health risk could be a problem that prevents the large-scale application of these nanomaterials.[31] For this reason, a number of research studies have been focused on the use of different structures, such as carbon nanomaterials. Carbon nanotubes, as well as graphene and its derivatives, have outstanding optical properties and have

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Table 1. Summary of Studies on the Use of Conjugated Polymer PTT Nanoplatforms in Cancer Polytherapies

polymer	wavelength of laser (nm)	laser power density (W cm^{-2})	radiation time (min)	temp. reached (°C)	cell line	animal model	ref
PNIPAM-dPG/PANI	785		20	42	A2780	female nude mice	51
FA−Lipid−PANI	808	2	5	50	HeLa	female BALB/c mice	52
PPy@BSA-Astx	808	1	5	57	MDA-MB-231		53
Ppy	1064	1	10	55	MDA-MB-231	BALB/c nude mice	54
PEG−PCL-C3-ICG	808	2	8	47	HSCs	nude mice	55
DPPV	808	0.3	5	51	4T1 and RAW264.7	BALB/c mice	56
ICG-PtTFPP	808	1	5	48	HepG2		57
PBTPBF-BT	1064	2	5	56.4	MDA-MB-231	female BALB/c nude mice	58
$DSPN_5$	808	1	6	60.9	4T1	BALB/c mice	59
T-TTQ/DOX	800	1	10	56	MDA-MB-231		60
PFVBT/PIDTTTQ	808	0.5	2	60	SKBR-3	nude mice	61
PorCP	808	0.75	10	66	HeLa and MDA-MB-231	zebrafish	62
N4	808	0.8	8	64	MDA-MB-231 and NIH-3T3		63
TBDOPV-DT	1064	0.98	1	107		pig skin	64
BBT-2FT	808	1.77	10	62	HeLa		65
PBIBDF-BT	808	1	10	55	MDA-MB-231	female BALB/c nude mice	66
PPor-PEG	630	0.8	10	50	HeLa	male nude mice	67
BDT-IID	660	0.2	10	58.8	MCF-7	male nude mice	68
DPP-DT	808	0.5	5	62	MCF-7 and HeLa	female nude mice	69

been indicated as potential therapeutic agents for PTT applications.[32] However, the practical application of one- and two-dimensional carbon nanomaterials for nanomedicine is still open to doubt because several studies have demonstrated their harmful effects on body tissues and cells due to their intrinsic toxicity and low biocompatibility.[33]

In light of potential advantages, the possibility of developing organic nanomaterials as PTT agents has recently attracted the attention of the scientific community (Figure 1b). Polymeric nanostructured materials have been widely applied in nanomedicine for various purposes such as tissue engineering,[34] drug delivery,[35] biosensors,[36] antibacterial materials,[37] and biointerfaces.[38] Several kinds of polymer nanomaterials possess the main requirements necessary to be considered as potential PTT agents: suitable size and shape, dispersibility in an aqueous medium, light-to-heat conversion of NIR radiation, photostability, low cytotoxicity, and accumulation in living tissues.[39,40] Polymer-based nanomaterials for PTT application are not only more biodegradable and remain in the body for shorter periods of time after systemic administration than inorganic nanoparticles[41] but they also offer indirect advantages because of their synthesis and the possibility to apply further forms of treatment with the aim of developing more advanced biomaterials.

Green chemistry is an area of chemistry focused on the development of sustainable technologies for the production of materials by chemical strategies. *Green polymer chemistry*, which is at the forefront of this innovative strand of work, has led to the development of a few encouraging viable synthetic strategies for suitable polymer synthesis.[42] Moreover, unlike inorganic nanomaterials, polymers can be easily processed using postsynthesis treatments for the preparation of nanomaterials with well-defined structures. Advanced techniques like electrospinning[43] and 3D-printing[44] have already been applied with great success to fabricate biomaterials for medical applications. Most importantly, tailored polymer-based nanomaterials could be designed to produce a cascade response to light stimulations.[45] Using this nature-inspired mechanism, light irradiation activates the material response (e.g., heat generation), which acts as a "mediator" to trigger structural polymer transformations (e.g., expansion/contraction, chain mobility, crystallinity, or material rupture) and in turn gives novel material functionalities such as on−off switching of drug/gene delivery or signals for imaging purposes. This unique and fascinating property makes it possible to develop multifunctional materials that are able to combine photothermal therapy with other targeted cancer diagnostic and therapeutic treatments.[46]

The main aim of this review is to summarize the potential of polymer-based nanomaterials as photothermal cancer therapeutic agents for targeted polytherapy. We summarize the recent results in designing, fabricating, and testing different types of nanostructures that show potential for developing multifunctional nanoplatforms thanks to their cascading responsiveness to light stimuli. Finally, we highlight the key points for the development of more effective nanomaterials and the emerging perspectives and challenges for future research from the viewpoint of material scientists.

2. CONJUGATED POLYMER NANOMATERIALS

Conjugated polymers (CPs) are an important class of macromolecules having the π-electrons system delocalized over the whole polymeric main chain. Since the discovery of the doping of polyacetylene, many other new polymers with a high structural versatility and stability in the neutral and the doped states have been successfully synthesized and applied in different fields such as batteries,[47] organic electronics,[48] and solar cells.[49] Moreover, these polymers have recently attracted great interest due to their biomedical applications.[50]

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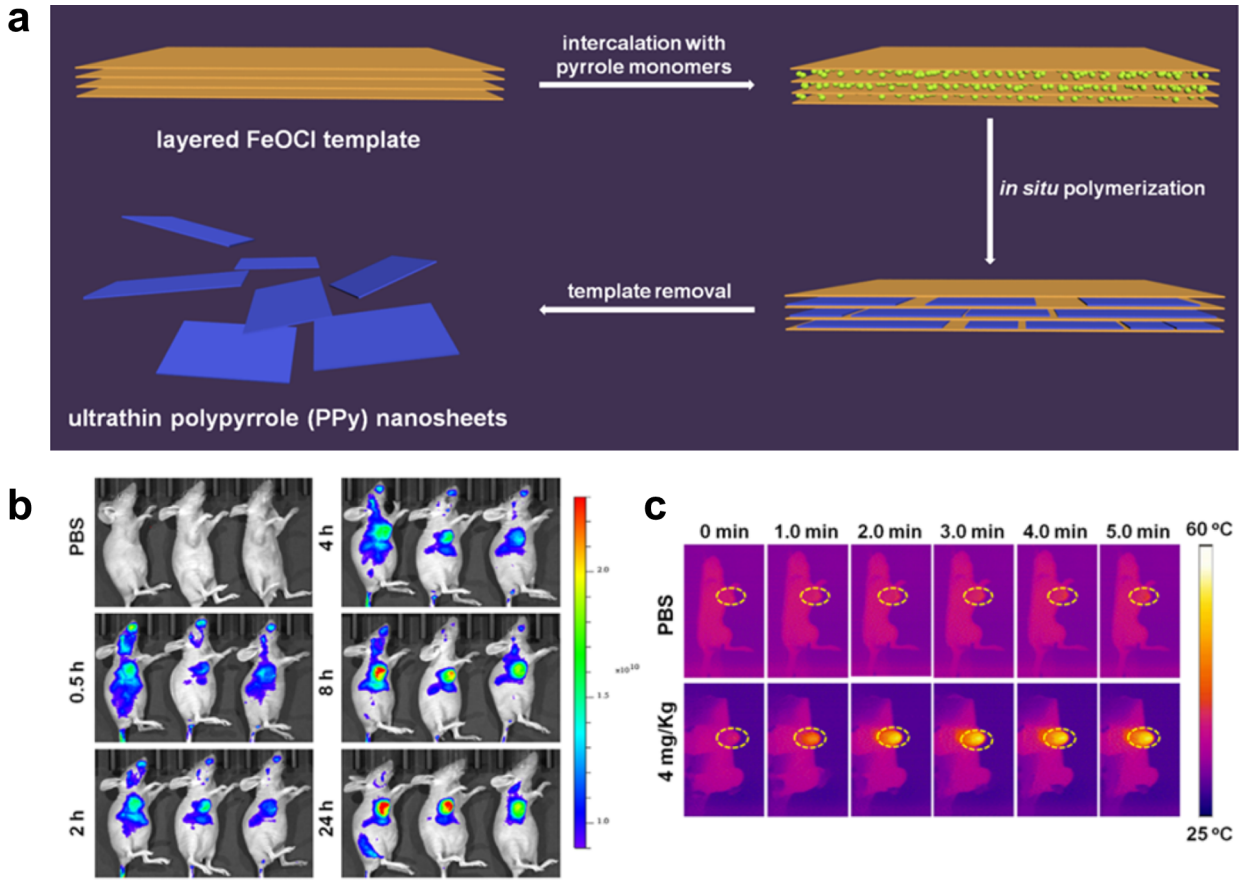

Figure 2. (a) Schematic illustration of the preparation of PPy nanosheets. (b) Fluorescent images at different time points post intravenous injection of PPy nanosheets. (c) Infrared thermographic images of tumor-bearing mice after intravenous injection of PBS and PPy nanosheets after irradiation by a 1064 nm laser. Reprinted with permission from ref 54. Copyright 2018, American Chemical Society.

Photothermal therapy exploits photoabsorbing agents that are able to efficiently convert the absorbed light into heat to induce local hyperthermia that results in irreversible damage to cancer cells. In a similar way, photodynamic therapy (PDT) uses photosensitizers to transfer coherent light energy to oxygen molecules, thus generating cytotoxic reactive oxygen species (ROS). Although photosensitizers for PDT can also be activated using visible light, an important prerequisite for PTT is the use of CPs that absorb in the NIR region (650−1700 nm) because blood and tissues absorb in the UV−vis spectral range. Recently, CPs have been successfully used for PTT and PDT in cancer thanks to their highly electronic-delocalized structures, which are particularly prone to absorbing light to be converted to heat, fluorescence, and other energies. Moreover, some CP nanosystems show photoacoustic (PA) effects. Basically, they are able to absorb light, creating a thermally induced pressure increase that generates ultrasonic waves (phonons). Phonons can be received by acoustic detectors to form high-resolution images of deep tumors.

A new important class of CPs is D−A copolymers, which have a combination of electron-rich (ED) and electron-deficient (EA) moieties in their conjugated backbone. They usually show very low band gap ($\pi-\pi^*$) energy and long wavelength absorptions. Photons in the NIR-II region (950−1700 nm) provide more efficient tissue penetration ability than NIR-I photons (650−950 nm) when considering absorption and scattering effects in tissues. Moreover, the structural versatility of CPs makes the insertion of specific chromophores, photosensitizers, or other functional groups of biological interest (in the polymer main chain or in side chains) particularly simple. CPs are usually hydrophobic materials, but they can be effectively coated by hydrophilic polymers to achieve water-dispersible nanoparticles (NPs) for biomedical applications. CP NPs can also be loaded with a variety of photothermal agents, metallic NPs, and anticancer drugs by conventional nanoencapsulation strategies. Herein, we describe some examples of photothermal (PT) and photodynamic (PD) therapeutic CP nanosystems together with recent developments in combinational drug-assisted therapy, and a summary of currently available studies involving the application of these multifunctional nanoplatforms is presented in Table 1.

2.1. Polyaniline. Polyaniline (PANI) can easily transit from emeraldine base (EB) state to emeraldine salt (ES) state in the presence of strong acids with a marked red-shift of its absorption maximum wavelength toward the NIR region. Molina et al. synthesized a thermoresponsive nanocomposite incorporating in situ-polymerized PANI.[51] The dendritic nanogel, based on poly(*N*-isopropylacrylamide) (PNIPAM) cross-linked with 33 wt % of dendritic polyglycerol (dPG), was swollen in a solution of aniline and polymerized using $(NH_4)_2S_2O_8$. The final interpenetrated nanogel showed an excellent compatibility in physiological environments, and in vivo studies showed that mice tolerated an accumulated dose of 500 mg kg^{-1}, which is able to inhibit A2780 tumor transplant growth by 55.3% after exposure to NIR laser light (distance: 5 cm, 5 min, 0.5 W maximum power). A simple method for preparing hybrid PANI

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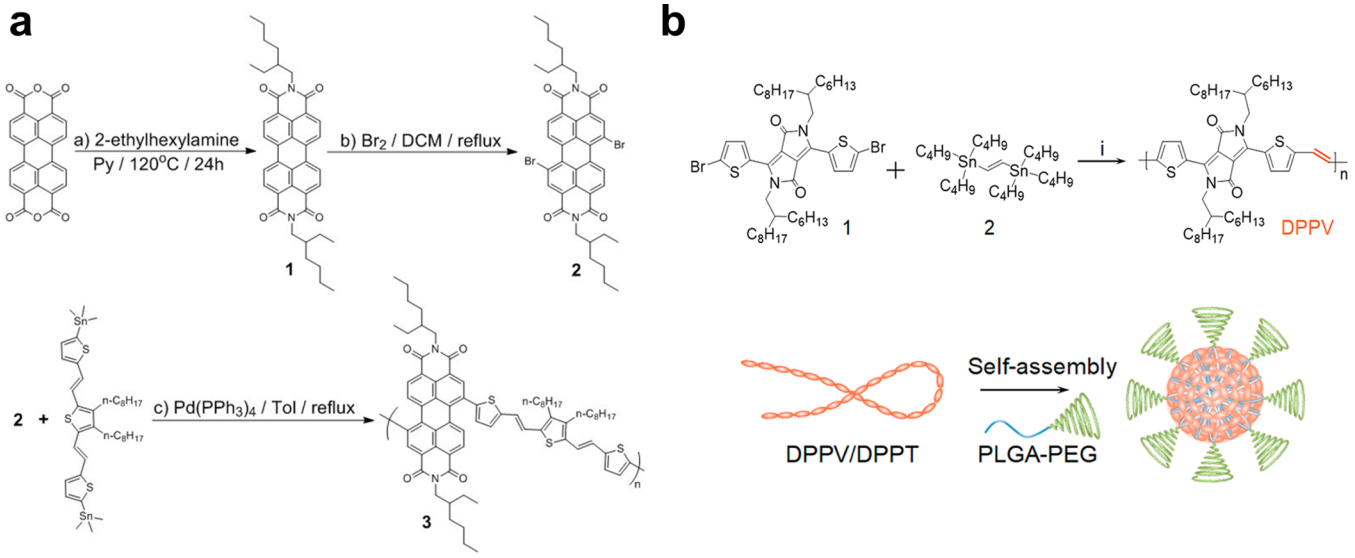

Figure 3. (a) Synthetic route of C3. Reprinted with permission from ref 55. Copyright 2017, American Chemical Society. (b) Synthesis of DPPV ((i) $Pd_2(dba)_3$ and tri(*o*-tolyl)phosphine, toluene, 100 °C, 24 h) and schematic illustration of DPPV/PLGA-PEG NPs. Reprinted with permission from ref 56. Copyright 2018, American Chemical Society.

NPs has been reported by Wang et al.[52] EB PANI was doped with *n*-dodecylbenzenesulfonic acid (DBSA), yielding ES PANI, which was dissolved in $CHCl_3$ and added to 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC). After solvent evaporation, the thin film of lipid-PANI NPs was conjugated with folic acid (FA) as the targeting ligand to enhance its tumor-targeting ability. FA-lipid-PANI NPs showed high biocompatibility and stability in physiological environments and, owing to the strong absorbance in the NIR region (λ_{max} = 810 nm) that is ascribable to the presence of polarons in the conjugated PANI backbone, showed a relatively high photothermal conversion efficiency (η = 25.6%) under laser irradiation at 808 nm. The in vitro cytotoxicity of NPs toward HeLa (human cervical cancer cells) reached nearly 70% at an NP concentration of 100 μg mL^{-1} under 808 nm irradiation. Moreover, the local tumor temperature of HeLa tumor-bearing BALB/c mice treated with tail injections of FA-lipid-PANI NPs rapidly increased up to 50 °C upon irradiation (@ 808 nm, 2 W cm^{-2}, 5 min), and the tumor was completely eliminated after 10 days.

2.2. Polypyrrole. Polypyrrole (PPy) is one of the most studied ICPs for PTT applications thanks to its strong absorbance in the NIR region. Recently, Bharathiraja et al. have developed PPy NPs using astaxanthin (Astx)-conjugated bovine serum albumin (BSA) as a coating agent (PPy@BSA-Astx).[53] They used Astx, a natural keto-carotenoid pigment, as a photosensitizer to generate reactive oxygen species (ROS) under 808 nm laser irradiation. At a power density of 0.3 W cm^{-2} for 15 min, they observed a significant reduction of MDA-MB-231 cell viability depending on the nanoparticle concentration, which is ascribable to the photodynamic toxic effect on breast cancer. Moreover, PPy@BSA-Astx NPs in water solution at 50 μg mL^{-1} concentration showed a high photothermal efficiency imputable to PPy, enabling the possibility to reach 57 °C in 5 min at 1 W cm^{-2} power density. NPs were also screened for ultrasound signal generation under 808 nm laser irradiation, revealing their ability to generate PA signals even at low concentrations (10 μg mL^{-1}). Because the NIR II window offers a high efficiency in tissue penetration owing to the reduced photon scattering and lower tissue background, Wang et al. recently prepared ultrathin PPy nanosheets with improved absorption at 1064 nm (ε = 27.8 L g^{-1} cm^{-1}) to be used as PT agents in the second NIR window (Figure 2).[54] PPy is a low-cost, biocompatible, photostable conjugated polymer that can be easily doped up to high levels with a controlled doping process by means of Fe(III) inorganic salts. A layered iron oxychloride template was used to obtain ultrathin PPy nanosheets in which the CP was in its doped, low-bandgap, high-wavelength absorption bipolaron state. The as-synthesized nanosheets were coated with 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)-2000] (DSPE-PEG2000), obtaining highly stable physiological dispersions for biomedical applications. PPy nanosheets exhibited high in vitro and in vivo photothermal ablation ability toward cancer cells in the NIR II window. Their photothermal conversion efficiency was 55.6% at 808 nm and even higher (64.6%) at 1064 nm; in vitro studies revealed that 80% of MDA-MB-231 human breast adenocarcinoma cells were killed when exposed to a 1064 nm laser beam (1.0 W cm^{-2}, 10 min). Moreover, the use of PPy nanosheets permitted the effective PT ablation of tumors in nude mice at depths of 8 and 6 mm by means of 1064 and 808 nm laser sources, respectively, suggesting promising applications of these nanomaterials for effective deep-tissue PTT.

2.3. Polythiophene. Polythiophene (PTh) derivatives usually exhibit excellent photostability, light-harvesting ability, easy synthesis, and facile functionalization with different substituents. Ren et al. successfully synthesized a new organic compound by covalently linking 2-*N*,*N*′-bis(2-(ethyl)hexyl)-perylene-3,4,9,10-tetra-carboxylic acid bis-imide to a thienylvinylene oligomer, obtaining a conjugated copolymer (C3) with excellent photothermal properties thanks to the presence of benzene rings and conjugated double bonds (Figure 3a).[55] C3 was coprecipitated with PEG-PCL and indocyanine green (ICG) to obtain encapsulated multifunctional nanospheres with an average diameter of 50 nm. When PEG-PCL-C3-ICG NP-distilled water solution was exposed to 808 nm laser irradiation for 10 min, the temperature increased from 25 °C up to 47 °C, confirming the strong PT effect. Moreover, multifunctional

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encapsulated NPs exhibited a low cytotoxicity and an efficient ROS production in vitro for PDT treatment of oral squamous cell carcinoma (OSCC). Additionally, HSC tumor-bearing mice injected with NPs and exposed to laser radiation (@808 nm, 2 W cm^{-2}, 8 min) showed a remarkable tumor volume reduction. The persistence of conjugated polymer nanoparticles (CPNs) could be a threat to the human body. In fact, an important challenge for the use of CPNs for in vivo theranostics is to prevent accumulation of nanoparticles in the body. Recently, Lyu et al. developed a biodegradable conjugated polymer that can be gradually broken down into small fragments in the presence of the oxidative species normally abundant in the biological environment.[56] In the synthesized poly{2,2′-[(2,5-bis(2-hexyldecyl)-3,6-dioxo-2,3,5,6-tetrahydropyrrolo[3,4-*c*]-pyrrole-1,4-diyl)-dithiophene]-5,5′-diyl-*alt*-vinylene} (DPPV) (Figure 3b), the presence of vinylene bonds in the main chain not only enhances its biodegradabilty and biocompatibility but also increases the photothermal conversion efficiency and the mass absorption coefficient for superior antitumor efficacy. Moreover, DPPV showed an intense PA activity for a more effective imaging capability. The PTT conversion efficiency of DPPV/PLGA-PEG NPs reached a notably high value of 71% (@ 808 nm, 0.3 W cm^{-2}), among the best values recorded for photothermal theranostic agents. The antitumor effect of DPPV PEGylated NPs was evaluated by measuring the volumes of tumors induced by injecting 4T1 mammary carcinoma cells in living mice, resulting in tumor growth that was effectively inhibited during the whole tested period. Finally, the ex vivo histological data provided evidence that no significant histopathological lesions or abnormalities were observed for the main vital organs of treated mice owing to the good biodegradability and organically benign composition of the employed CPNs.

2.4. CPs Containing Organic Light-Absorbing Dyes. Porphyrins are strong light-absorbers, showing an absorption band around 400 nm (Soret band) and two Q-bands around 510 and 540 nm. Recently, Wang et al. reported on the synthesis of polymeric NPs loading ICG, Pt(II)-meso-tetra-(pentafluorophenyl)porphyrine (PtTFPP) and poly(9,9-di-*n*-octylfluorenyl-2,7-diyl) (PFO) (Figure 4).[57] The simultaneous presence of a photosensitizer (PtTFPP), an organic semiconducting polymer acting as two-photon antenna (PFO), and a NIR-absorbing photothermal dye (ICG) in the same nanoparticle led to a strong photothermal performance under 808 nm laser irradiation and a high $^1O_2$ generation efficiency under NIR light exposition, thus making the assembled multifunctional therapeutic nanoplatform particularly promising for cancer treatment.

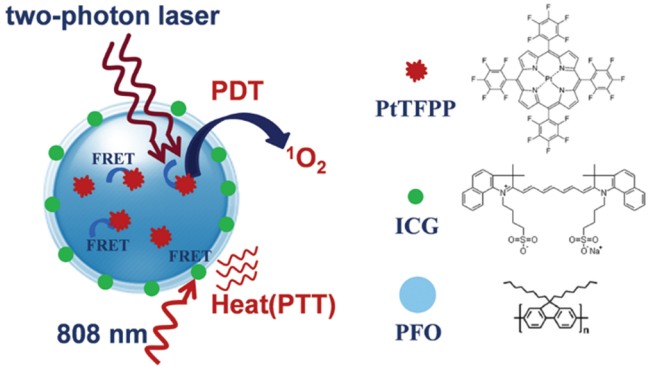

Figure 4. Schematic illustration of multifunctional ICG-PtTFPP NPs. Republished with permission of Royal Society of Chemistry from ref 57, Copyright 2017; permission conveyed through Copyright Clearance Center, Inc.

2.5. D−A Conjugated Polymers. D−A conjugated polymers are very useful materials for photothermal cancer therapy. Indeed, their HOMO−LUMO gap can be easily tuned by the choice of suitable electron donor/electron acceptor moieties. Cao et al. recently designed a thieno-isoindigo derivative-based semiconducting polymer, PBTPBF-BT, in which the bis(5-oxothieno[3,2-*b*]pyrrole-6-ylidene)-benzodifurandione (BTPBF) and the 3,3′-didodecyl-2,2′-bithiophene (BT) units acted as EA and ED, respectively (Figure 5a).[58] The polymer, with a very low bandgap (1.24 eV) and a λ_{max} at 1107 nm, was formulated into nanoparticles using an amphiphilic diblock copolymer to enhance its solubility in aqueous environments. The obtained NPs showed a spherical morphology with a diameter of ∼45 nm and a remarkable mass extinction coefficient of 89.3 mL cm^{-1} mg^{-1} at 1064 nm in the NIR II region. NPs have been evaluated as PT agents by exposing MDA-MB-231 cells to a 1064 nm laser at a power density of 0.42 W cm^{-2}. After 10 min, more than 50% of the cancer cells were killed using an NP concentration of 3.75 μg mL^{-1}. In vivo activity was tested on MDA-MB-231 tumor-bearing mice that were injected with a PBTPBF-BT NP dose of 30 μg per mouse and exposed to 1064 nm laser light for 10 min at 0.42 W cm^{-2}. The tumor growth was completely inhibited, and only black scars were observed at the original tumor sites at 14 days post-treatment. Jiang et al. synthesized a conjugated copolymer with alternated cyclopentadithiophene (ED) and benzothiadiazole (EA) units. Hydrophilic PEG chains were grafted onto a hydrophobic CP backbone leading to water-soluble NPs.[59] The presence of CP in NPs gave them some important properties: intense PT activity, strong NIR fluorescence, and the ability to interact with the aromatic anticancer Doxorubicin (DOX) through hydrophobic $\pi-\pi$ interactions. Yuan et al. also described the preparation of a multifunctional nanoplatform by combining DOX with a PT-conjugated polymer based on thiadiazoloquinoxaline EA units alternated with functionalized fluorene ED units.[60] The use of a NIR laser-responsive amphiphilic brush copolymer as the encapsulation matrix allowed for efficient phototriggered drug release. The obtained NPs were also surface-modified with cyclic arginine-glycine-aspartic acid (cRGD) tripeptide to increase their accumulation within cancer cells. Feng et al. designed an organic NP-based theranostic platform using two D/A copolymers: poly[9,9-bis(2-(2-(2-methoxyethoxy)ethoxy)-ethyl) fluorenyldivinylene]-*alt*-4,7-(2,1,3-benzothiadiazole) (PFVBT) with bright red fluorescence and high ROS production and poly[(4,4,9,9-tetrakis(4-(octyloxy)phenyl)-4,9-dihydros-indacenol-dithiophene-2,7-diyl)-*alt*-co-4,9-bis-(thiophen-2-yl)-6,7-bis(4-(hexyloxy)phenyl)-thiadiazolo-quinoxaline] (PIDTTTQ) with broad absorption in the NIR region.[61] The two copolymers were coencapsulated to form CP NPs using a PEG matrix, and an anti-HER2 affibody was attached to the nanoparticle surface through surface conjugation. The obtained multifunctional theranostic NPs showed high fluorescence (η = 23%) and light-to-heat conversion efficiency (47.6%) and an excellent targeting ability toward HER2-overexpressed SKBR-3 breast cancer cells. A D−A porphyrin-containing conjugated polymer showed the absorption peak at 799 nm, good biocompatibility and photostability, and a very high PT conversion efficiency (63.8%).[62] The in vitro

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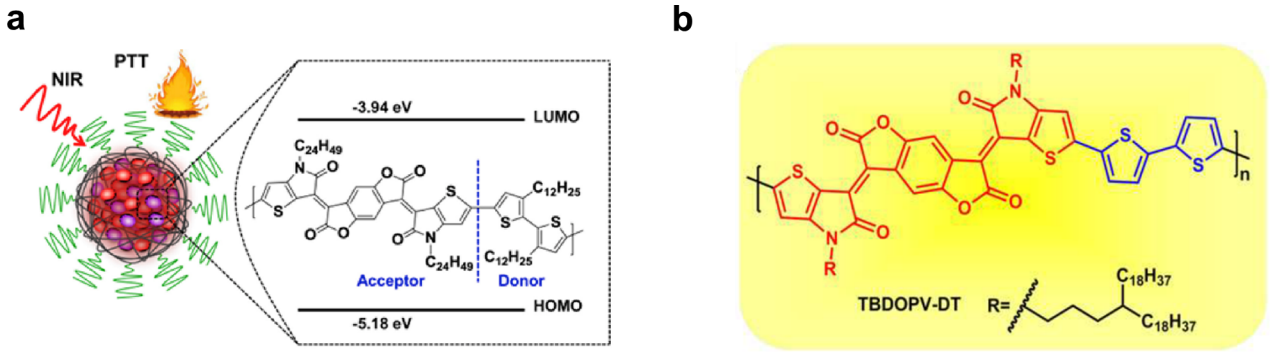

Figure 5. (a) Schematic illustration of PBTPBF-BT NPs. Reprinted from ref 58. Copyright 2017, with permission from Elsevier. (b) Chemical structure of TBDOPV-DT polymer. Reprinted with permission from ref 64. Copyright 2016, American Chemical Society.

cancer cell ablation activity of its NPs was satisfying because, at a concentration of 5 mg L^{-1}, almost 80% of MDA-MB-231 human breast cancer cells were killed under laser irradiation at 0.75 W cm^{-2} for 10 min. Conjugated oligomers often exhibit a better-defined structure and a higher degree of purity and synthetic reproducibility than those of their conjugated polymer analogues. Cai et al. recently developed novel D−A conjugated oligomer-based NPs with high PT activity and biocompatibility and an excellent contrast when used for PA imaging of sentinel lymph nodes.[63] An efficient NIR II PT conversion was obtained using the new D−A conjugated polymer TBDOPV-DT.[64] It contained a thiophene-fused benzodifurandione-based oligo(*p*-phenylenevinylene) (TBDOPV) as EA unit and 2,2′-bithiophene (DT) as ED moiety (Figure 5b) and showed an absorption peak at a very long wavelength (1093 nm), high biocompatibility, and highly efficient photothermal conversion through 0.2 cm of pig skin tissue (33% of transmittance).

Huang and co-workers reported on the synthesis of a theranostic agent based on benzo[1,2-*c*,4,5-*c*′]bis[1,2,5]-thiadiazole-4,7-bis(9,9-dioctyl-9*H*-fluoren-2-yl)thiophene (BBT-2FT) to take advantage of the high EA characteristics and strong light absorption of benzo-bis-thiadiazole (BBT) derivatives.[65] The conjugated molecule contained fluorene moieties as ED groups and a BBT unit as electron-acceptor. The presence of hypervalent sulfur atoms in quinoidal structures in the conjugated backbone ensured high NIR absorption in the NIR II therapeutic optical window. By coprecipitating the conjugated molecule in the presence of the block copolymer PEG-*b*-PCL, they obtained BBT-2FT NPs, which showed high PA signal intensity and PT conversion efficiency (η = 40%). When CPs are encapsulated into NPs and suspended in aqueous media, their aggregation can reduce the overall fluorescence and ROS generation ability. However, some types of weakly emissive NPs show the opposite phenomenon, being induced to emit by aggregate formations. Another D−A conjugated polymer architecture for PTT was proposed by Li et al.[66] PBIBDF-BT copolymer showed in its structure the EA isoindigo derivative bis(2-oxoindolin-3-ylidene)-benzodifuran-dione (BIBDF) and the ED unit bithiophene (BT). NPs were obtained by emulsifying the conjugated polymer with the amphiphilic copolymer mPEG-*b*-PHEP and showed a high antitumor efficiency toward MDA-MB-231 tumors in mice by irradiation (808 nm, 0.5 W cm^{-2}, 10 min). A higher activity was reached when PBIBDF-BT NPs were coloaded with doxorubicin because NIR irradiation was capable of efficiently triggering DOX release from PBIBDF-BT@NP_{PPE}/DOX nanoparticles. Combining D−A conjugated polymer with wide-absorption organic dyes can be an efficient way to improve the light-absorbing ability of the polymer to further enhance its theranostic properties, especially for PT applications. Recently, for the first time, Zhang et al. introduced a light-harvesting unit on a D−A polymer.[67] The semiconducting polymer was obtained by the copolymerization of 5,6-difluoro-4,7-bis[5-(trimethylstannyl) thiophen-2-yl]benzo-2,1,3-thiadiazole as an EA and 5,5′-dibromo-4,4′-bis(2-octyldodecyl)-2,2′-bithiophene as an ED in the presence of a porphyrin-pyrene pendant as a side-branch unit. The obtained copolymer was nanoprecipitated with HOOC-PEG-COOH and $PMHC_{18}$-mPEG copolymers to increase the water dispersibility and size stability of the resulting biocompatible electron D−A conjugated semiconducting polymer NPs. As expected, the spherical-shape NPs showed a very high photothermal conversion (η = 62.3%) and a strong fluorescence for PA imaging-guided PTT. Mice injected with A549 human lung cancer cells achieved 100% tumor elimination using a dose of 15 mg kg^{-1} of NPs under laser irradiation (630 nm, 0.8 W cm^{-2}, 10 min). Although many polymeric photothermal agents have shown great potential for cancer treatment, they are often assembled in unstable nanostructures that can degrade in short times. Chang et al. recently synthesized a new D−A copolymer: 4,8-bis[5-(2-ethylhexyl)thiophen-2-yl]-2,6-bis(trimethylstannyl)benzo[1,2-*b*,4,5-*b*′]dithiophene-6,6′-dibromo-*N*,*N*′-(2-ethylhexyl)isoindigo (BDT-IID) with strong absorption in the 650−700 nm range.[68] Polymer dots, with spherical morphology and an average diameter of 18 nm, were obtained by coprecipitating BDT-IID and poly(styrene-*co*-maleic anhydride) (PSMA). Polymer dot (Pdot) aqueous dispersions were very stable, and no aggregation was observed even after 30 days, whereas they showed enhanced photostability. NP dispersions in water at a concentration of 100 μg mL^{-1} were irradiated using a laser source (@ 660 nm, 200 mW cm^{-2}) reaching a temperature of 53.2 °C after 600 s. Even after seven irradiation cycles, the Pdots still maintained the ability to increase the temperature to the same level, denoting an excellent photostability of the employed chromophoric system. Moreover, because the measured photothermal conversion efficiency was particularly high (45%), the prepared nanomaterials were also examined as PT agents for tumor therapy. Animal tests were carried out on MCF-7 tumor-bearing mice injected with BDT-IID Pdots and subjected to irradiation under the previously described conditions. The results showed marked tumor inhibition when compared to the control group mice. More importantly, no appreciable signs of organ damages or inflammatory lesions could be observed on major organs as a consequence of the PTT treatment. All the aforementioned

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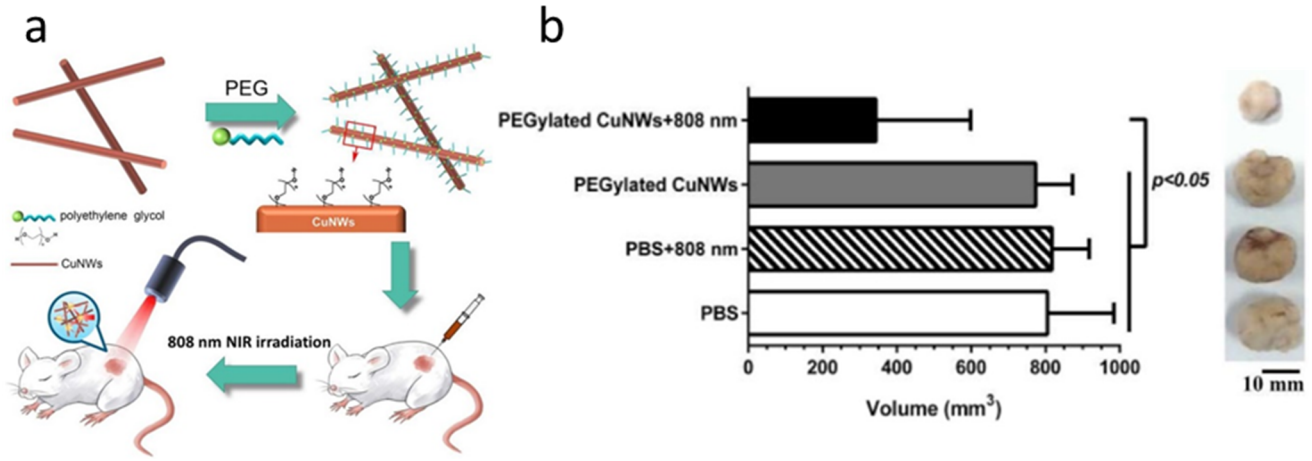

Figure 6. (a) Scheme representing the use of PEGylated copper nanowires as a photothermal agent for cancer therapy. (b) Tumor volume of CT26-bearing BALB/c mice after PEGylated copper nanowires after photothermal ablation. Reprinted with permission from ref 77. Copyright 2016, American Chemical Society.

results demonstrated that the BDT-IID Pdots are particularly promising for nanotheranostic applications. A few novel nanoplatforms based on Pdots for tumor phototherapy have been developed by the Wu research group.[69,70] Recently, Chen et al. designed a conjugated polymer-based nanocarrier for enhanced anticancer PTT by integrating a diketopyrrolopyrrole-dithiophene (DPP-DT) derivative with an amphiphilic polymer (polystyrene-grafted ethylene oxide functionalized with carboxyl groups) used as the encapsulation matrix.[69] DPP-DT NPs (Pdots) were prepared starting from semiconducting polymer solutions at different concentrations, observing that NPs with larger sizes were recovered when the concentration of the solution was increased. Interestingly, the wavelength of the absorption peak of Pdots was strongly dependent on their size and also on the molecular weight of the semiconducting polymer. This very versatile system was capable of tuning its optical absorption by simply acting on particle morphology and on the mean conjugation length of the conjugated polymer. PEGylated polymer dots showed high PT conversion efficiency (>50%), photostability, and therapeutic performance. Mice bearing H22 or 4T1 tumors were injected with coated Pdots (1.0 mg kg^{-1}) and subsequently exposed to laser irradiation (@ 808 nm, 0.5 W cm^{-2}, 5 min), and tumor growth was strongly inhibited, leaving only black scars at the original tumor sites, which faded in ∼10 days.

Fluorescence imaging technique, offering high temporal resolution, safety, and sensitivity at low cost, has been extensively investigated for the purpose of diagnostics and therapy of diseases. Conjugated Pdots have been widely accepted as a promising class of fluorophores due to their intense brightness and nontoxic features. Moreover, these particles could emit in the NIR region acting as local sources of activation for PTT agents. Wu et al. synthesized polymer-blended Pdots of a green-light-harvesting polymer (poly[(9,9-dioctylflurenyl-2,7-diyl)-*co*-(1,4-benzo-{2,1′,3}-thiadiazole)] (PFBT)) as the ED unit and a deep-red emitting polymer (poly[(9,9-dioctylflurenyl-2,7-diyl)-*co*-(4,7-di-2-thienyl-2,1,3-benzothiadiazole)] 95:5 (PF-DBT5)) as the EA unit.[71] Pdots showed high absorption in the visible range and high quantum yield in deep-red emission. PF-DBT5, PFBT, and an amphiphilic polymer (PSMA) were co-condensed, giving highly fluorescent polymeric blend dots (PBdots) that exhibited a quantum yield of 0.56, the highest value reported so far for polymer dots. PBdots were then covalently conjugated to the peptide ligand CTX, a tumor-targeting agent with a strong affinity for neuroectodermal tumors. PBdots-CTX were able to traverse the blood-brain barrier and selectively target ND2:SmoA1 tumors in mice. They also proved to be photostable during in vivo fluorescence signal recording, but no evident fluorescence was observed in mouse blood 72 h after injection, indicating a good clearance of this new type of NP platform. Among fluorescence imaging techniques, NIR fluorescence has been successfully employed for clinical image-guided cancer surgery. In fact, NIR fluorescent probes (λ>700 nm) are particular promising because they allow in vivo bioimaging with high penetration depth and minimal auto-fluorescence interference. Chen et al. developed a novel semiconducting polymer by incorporating a NIR emissive porphyrin unit and other monomers into one polymeric backbone using Suzuki coupling reaction.[72] The aim of the authors was to obtain a new polymeric system with a large absorption coefficient in the visible region and efficient promotion of the cascade energy transfer to the NIR unit. The synthesized polymer (NIR800), showing an intense emission at 800 nm with a narrow bandwidth, was further blended with (poly[(9,9-dioctylflurenyl-2,7-diyl)-*co*-(4,7-bis(4-hexylthiophen-2-yl)-2,1,3-benzothiadiazole)] (PFDHTBT) as a donor polymer to enhance the energy transfer via Förster mechanism. The blended Pdots showed a broad absorption range (from 500 to 600 nm) and an enhanced quantum yield (15%) for the narrow band emission. The PEGylated Pdots evidenced a long blood circulation time and selectively accumulated in the lymph nodes and tumors, allowing for obtaining high resolution fluorescence mapping for image-guided surgery.

3. POLYMER-FUNCTIONALIZED NANOPARTICLES

Polymer functionalization of nanoparticles is a widely used technique for stabilizing biomaterials and preventing their aggregation. In the case of metal and semiconducting nanoparticles, the interparticle attractive forces are especially strong. Moreover, it is very important to prevent the attractive interactions of such nanoparticles with the components found in body tissues. This is why these nano-objects should be fully dispersed and stable. Polymer functionalization is a successful strategy for enhancing the stability of colloidal dispersions.[73] Several coating strategies of functionalization using polymers are

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well-known. One of the most useful strategies is the end-grafting of polymer chains onto the nanomaterial surface. The formation of a polymer brush at the colloidal interface is one of the most efficient methods used for colloidal dispersion stabilization.[74]

In this section, we focus on the functionalization of nano-objects by using different kinds of polymers that help to improve the chemical, physical, and biological properties of nanomaterials for photothermal therapy and endow the synthesized materials with novel and unexpected functionalities.

3.1. PEGylation. Nanomaterial functionalization with poly(ethylene glycol) (PEG) is one of the most common methods used to modify the surface of nanoparticles and give them stability in water, biocompatibility, and other interesting features. The literature has many examples of the use of this polymer to functionalize particles for biomedical applications.[75] Some of them have shown that, during in vivo tests, nanoparticles functionalized with PEG demonstrate remarkable properties such as reduced clearance through the reticuloendothelial system of the organism and passive targeting of tumors because of the enhanced permeability and retention effect. Similarly, PEGylation allows a long circulation time for NPs in the bloodstream,[76] whereas on the other hand, this technique is not useful for developing multifunctional nanomaterials for polytherapy applications. These functionalized particles have been investigated in numerous studies to prove their effective use as active agents for photothermal therapy.

Li et al. proposed PEG-functionalized copper nanowires as new photothermal therapy agents.[77] The PEGylation chemical process consisted of adding 200 mg of PEG to 15 mg of copper nanowires dispersed in 15 mL of THF. The mixture was stirred at 50 °C for 4 h. The functionalized nanomaterials have been characterized by higher flexibility than uncoated wires, and after implantation, they are intertwined around cancer cells. Thanks to this, the irradiated material transmits the generated heat to cells and effectively causes cancer ablation (Figure 6a). Tests have been conducted on colon tumor-bearing mice. PEGylated nanomaterials have been intratumorally injected and NIR irradiation conducted by using a NIR laser (808 nm) with a power density of 1.5 W cm^{-2}. After 6 min of irradiation, the temperature increased rapidly above 50 °C, and suppression of tumor growth and necrosis was observed (Figure 6b).

O'Neal and co-workers used PEG-coated nanoshells for treating murine colon carcinoma cells.[78] For the preparation of PEGylated nanoshells, PEG with a terminal thiol group was added to gold-silica nanoshells in deionized water. After the intravenous injection of PEGylated nanoshells and their 6 h circulation in the body, the mice were illuminated with a 808 nm diode laser (4 W cm^{-2}) for 3 min. During the first 30 s, the temperature reached 50 °C. After 10 days of nanoshell treatment, a complete resorption of the tumor was observed. At 90 days post-treatment, all mice were healthy and without tumors. Similarly, gold nanoshell agents functionalized with PEG have been developed by Hirsch et al.[79] Yang et al. have studied the possibility of using PEGylated conjugated nanographene sheets for the photothermal therapy of murine breast tumors.[80] The PTT agent preparation included the attachment of amine-terminated branched PEG to graphene oxide sheets via amide formation. Mice have been treated with 20 mg kg^{-1} of PEGylated nanosheets. After exposure to 2 W cm^{-2} of 808 nm NIR laser, the tumor surface temperature increased up to 50 °C. The authors demonstrated that this treatment completely eliminated 4T1 murine breast tumors and led to 100% mouse survival. In comparison to nonfunctionalized gold nanorods, the properties of PEGylated nanosheets seem to be similar in terms of administration routes (intravenous), injected doses (20 mg/kg), NIR laser density requirements (2 W cm^{-2}), and irradiation term (5 min). Interestingly, in vivo tests also show relatively low retention in reticuloendothelial systems and highly efficient passive tumor targeting.

Cyanine (Cy) is an organic dye with a high extinction coefficient in the NIR window that has been widely adopted as a drug in PTT therapy. Lin et al. prepared a poly(heptamethine) Cy-containing derivative (CyP) using a one-pot multicomponent reaction.[81] CyP was encapsulated into NPs using PEG-PLA copolymer obtaining high Cy-loading nanospheres with an average diameter of 50 nm. CyP@PEG-PLA NPs were stable in aqueous solutions for half a year, showed a PT conversion of 12%, and caused irreversible tumor cellular damage in mice with HeLa tumors upon 808 nm light irradiation for 30 min after injection of 150 μL of a 200 μg mL^{-1} NP solution.

3.2. Chitosan-Functionalized Nanomaterials. Chitosan is a natural cationic polymer characterized by properties that are significant for biomaterials: nontoxicity, biodegradability, and biocompatibility. Chitosan functionalization of nanoparticles for PTT has several advantages. Indeed, chitosan coatings protect nanoparticles, avoiding irreversible coalescence and improving their optical stability, thus rendering photothermal ablation more effective. The chitosan-based coating significantly changes the surface properties of nano-objects. Chitosan is an excellent agent for nanoparticle biocompatibilization and stabilization, but it can also be useful as a scaffold structure for anchoring the antibodies and proteins needed for selective cellular targeting.[82] Thanks to the presence of amino groups, chitosan can be applied to drug or DNA delivery systems because it can be ionically cross-linked to multivalent elements. Because of its properties, chitosan has already been widely used for coating metal nanomaterials such as gold and silver nanoparticles.[83]

Boca et al. focused on the study of photothermal activation in chitosan-coated silver nanotriangles (Chit-AgNTs) for treating human lung cancer cells (NCI-H460).[82] Chit-AgNTs have been prepared by triggering the reaction of silver nitrate in chitosan solution. Cells have been incubated with Chit-AgNTs and irradiated by a laser at different power densities for 10 min at 800 nm. The authors found that the rate of cell mortality in the presence of Chit-AgNTs was higher than in the presence of thiolated poly(ethylene) glycol-capped gold nanorods. Cytotoxicity tests have shown that Chit-AgNTs are efficiently taken up by cancer cells while exhibiting good biocompatibility for healthy human embryonic cells.

Zhuang et al. synthesized gold nanoparticles coated with chitosan or *O*-carboxymethyl chitosan (CMCS) and studied them as therapeutic agents for the photothermal ablation of cancer cells, such as the hepatocellular carcinoma cell line (HepG2) and human dermal fibroblast cells (HDF).[84] The particle functionalization procedure relies on mixing chitosan or CMCS with as-synthesized gold particle suspensions. During in vitro tests, HepG2 and HDF cell lines were incubated in a medium containing CN or CMCS gold nanoparticles for 2 h. The cells were exposed to 817 nm NIR laser (5 W cm^{-2}) for 2 min. The highest efficiency of the photothermal ablation was observed for the cells treated with gold/chitosan nanoparticles. Almost 100% of HepG2 and 90% of HDF cells were killed after the laser treatment.

3.3. Peptide Functionalization of Nanoagents. The diagnosis and treatment of cancer diseases at the cellular level would be greatly enhanced by the ability of multifunctional

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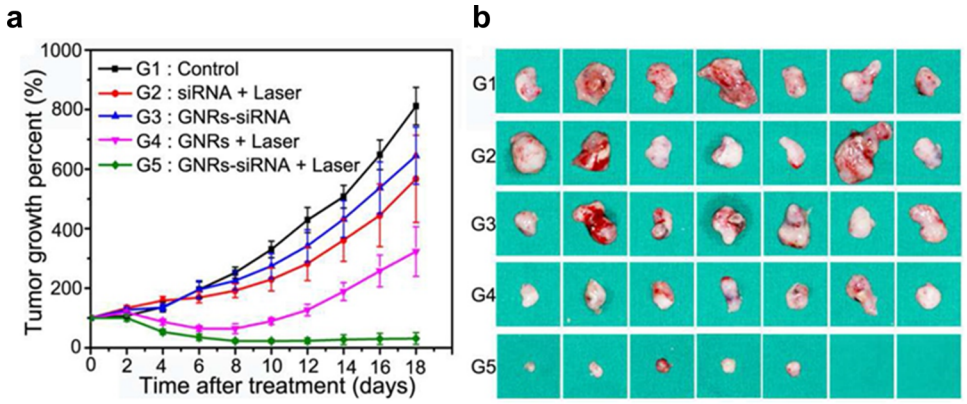

Figure 7. (a) Tumor growth percentage from different groups during the first 18 days after gold nanorod-siRNA treatment. (b) Photographs of tumors 18 days after G1−G5 treatments. Reprinted from ref 90. Copyright 2015, with permission from Elsevier.

nanomaterials to deliver active probes and therapeutic agents into specific cells and cellular compartments. The cell nucleus is the most desired target for cancer therapies. Targeted nuclear delivery of diagnostic probes and therapeutics could improve disease detection and treatment. The goal of several research studies is to further examine the ability of multipeptide nanoparticle conjugates to target cell nuclei. Observations suggest that the most efficient nuclear targeting may result from the use of peptides attached to a single vector. Combining this type of strategy with other types, such as photothermal therapy, offers greater possibilities for developing effective cancer cell eradication methods. Peptide layers screen the undesirable inorganic surface of nanoparticles behind an organic shell, endowing the nanoagents with the needed cell-entering properties together with the required optical properties.[73]

Daniels et al. have presented new approaches for the synthesis of pH Low Insertion Peptide (pHLIP) and PEG-coated spherical and spiked gold nanoparticles for the enhancement of radiation damage during NIR thermal therapy.[85] It has been shown that pHLIP peptides are excellent for targeting acidic tumors, and their use makes it possible to deliver therapeutic agents specifically to the cancer cells inside tumors. Irradiation by an 805 nm laser of multispiked gold nanoparticles coated with PEG and pHLIP led to a time- and concentration-dependent increase in temperature. The developed pHLIP-coated nanoparticles can find applications in targeted photothermal therapies of tumors.

The possibility of fabricating graphene oxide decorated with gold nanoparticles by using thermostable antimicrobial nisin peptides as functionalizing agents has been presented by Otari et al.[86] This nanocomposite has been used as an agent in photothermal therapy, showing enhanced photothermal activity compared to that of gold nanoparticles thanks to the presence of reduced graphene oxide (rGO). Nisin peptide has a wide range of antimicrobial activities against Gram-positive microorganisms. During in vitro tests, cells have been treated with the synthesized nanocomposite and irradiated using an 800 nm laser (at a power density of 0.5 W cm^{-2}). The photothermal effect of nanocomposites on MCF7 breast cancer cells caused the inhibition of ∼80% of the cells after 5 min of irradiation.

Tan et al. demonstrated that the lycosin-I-conjugated spherical gold nanoparticles (LGNPs), lycosin-I-modified gold nanorods (LGNRs), and gold nanorods (GNRs) showed efficient cellular internalization efficiency toward cancer cells, also displaying an unprecedented selectivity over noncancerous cells.[87] LGNRs and LGNPs have been examined as platforms for cancer photothermal therapy. In vitro tests have been carried out using HeLa cells previously incubated with LGNRs or peptide-modified gold nanorods (PGNRs) and near-infrared irradiation (808 nm) at a power density level of 2 or 5 W cm^{-2}. In vivo experiments using BALB/c nude mice with xenografted tumors were performed by intravenously injecting LGNRs, PGNRs, and sterile PBS three times with a time interval of 3 days. The cancer sites of each mouse were irradiated by a 808 nm laser at a power density of 3.54 W cm^{-2} for 5 min at 24 and 48 h after each injection. LGNRs exhibited selective intracellular translocation toward cancer cells and an efficient photothermal effect under near-infrared (808 nm) irradiation, which consequently effectively killed cancer cells in vitro and in vivo. Therefore, the established LGNPs and LGNRs possessed great potential in cancer-targeted delivery and photothermal therapy.

3.4. Functionalization with Nucleic Acids. The functionalization of nanoparticles with nucleic acids has many advantages, offering the possibility to combine photothermal therapy with gene therapy.[88] The aim of gene therapy is to treat cancer by using nucleic acids to inhibit the expression of genes that drive tumor progression. Small interfering RNA (siRNA) is one of the main types of nucleic acids useful in gene regulation. Its function is the suppression of gene expression, which triggers the degradation of RNA molecules inside the cytoplasm of cells. In this way, the production of the encoded disease-associated protein is stopped.[89]

Nanomaterial surface functionalization with siRNA has been used in the study presented by Wang et al.[90] They modified gold nanorods using siRNA, and the developed photothermal agent showed the ability to deliver siRNA oligos targeting the BAG3 gene, which efficiently blocked the heat-shock response. Gold nanorod-siRNA agents have been prepared by combining anionic-charged siRNA oligos with gold nanorods whose surface was previously modified by negatively charged poly(sodium 4-styrenesulfonate) (PSS) and positively charged poly(diallyldimethylammonium chloride) (PDDAC). In in vitro experiments, Cal-27 cells have been treated with functionalized gold nanorods for 24 h and irradiated by a 810 nm wavelength laser at different power densities. In the case of in vivo tests, mice infected with tumors have been injected with a gold nanorod-siRNA sol and irradiated by the 810 nm laser with a energy density of 600 J cm^{-2}. Eighteen days after the treatment, the tumors were extracted and analyzed (Figure 7). In vitro and in vivo studies demonstrated the ability of the siRNA-function-

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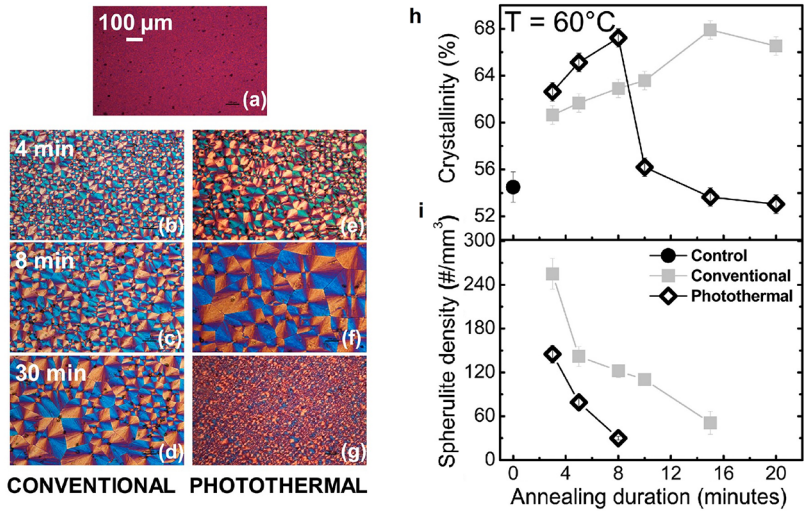

Figure 8. Images of poly(ethylene oxide) (PEO) spherulites observed through a cross-polarized optical microscope of (a) melt-crystallized gold nanoparticle:PEO film, (b–d) after conventional annealing at 60 °C and after the photothermal process, (e–g) at different time points, (h) crystallinities, and (i) spherulite densities as a function of annealing time for gold nanoparticle:PEO melt-crystallized films. The annealing was conducted by conventional and photothermal heating. Reprinted with permission from ref 103. Copyright 2013, American Chemical Society.

alized nanomaterials to overcome thermoresistance and produce the maximal tumoricidal effect with minimal damage to normal tissues. The inhibition of BAG3 expression makes cancer cells more vulnerable to chemo- and radiotherapy, thereby eliminating their therapeutic resistance and enhancing therapeutic efficacy.

Braun and co-workers used gold nanoshells modified with siRNA for gene silencing. They used a NIR laser to control the release of siRNA from nanoshells.[91] It has been shown that the intense local heating by pulsed lasers causes vesicle rupture, which allows for drug delivery through the membranes. To study the system efficiency, the authors used a GFP-expressing cell line, and the combination of siRNA release with nanoshell-induced endosome rupture was explored. Cells incubated with nanoshell-siRNA have been irradiated by an 800 nm pulsed laser with a power density of 3.5 W cm^{-2}. All samples showed high viability, but the GFP level for the laser-exposed nanoshell-siRNA showed gene silencing of ∼80% .

The use of pulsed near-infrared laser irradiation for the release of nucleic acids from gold nanoparticles has also been investigated by Takahashi et al.[92] They used plasmid DNA immobilized on gold nanorods modified by phosphatidylcholine (PC-GNRs). DNA-PC-GNR sols were irradiated with a 1064 nm laser. The results showed that only tens of seconds of NIR laser irradiation are necessary to induce DNA plasmid release. Such a rapid release is very beneficial for minimizing unwanted photochemical damage.

Another exciting application of photothermal therapy combined with gene therapy is the possibility to treat not only cancer, but also diseases caused by microbial infections. The use of aptamer-functionalized gold nanoparticles (Apt@Au NPs) and gold nanorods (Apt@Au NRs) for the inactivation of Methicillin-resistant *Staphylococcus aureus* (MRSA) by targeted photothermal therapy has been reported by Ocsay et al.[93] The DNA aptamer was specifically selected for MRSA cells and used for targeted therapy. Au NRs and Au NPs acted as convertors for transducing NIR radiation to heat for the photothermal inactivation of cells. Mixtures of aptamer-functionalized nanoparticle or nanorod sols and the cell solution were incubated for 1 h and then illuminated using a single-mode NIR laser with 808 nm wavelength at 1.1 W cm^{-2} power density. The results showed that both Apt@Au NPs and Apt@Au NRs specifically bound to MRSA cells but that only Apt@Au NRs effectively inactivated MRSA cells through hyperthermia due to their longitudinal absorption of NIR radiation and photothermal conversion. The authors also observed that the MRSA Apt@Au NRs are very effective and promising nanosystems for specific cell recognition and in vitro PTT. Au NRs have multiple functions, serving as a nanoplatform for aptamer immobilization and also providing multivalent effects for increasing the binding strength of the aptamer for the targeting of MRSA cells; moreover, they act as photothermal agents to inactivate cells with the heat generated under NIR irradiation.

The functionalization of nanoparticles used in photothermal therapy offers the possibility of combining this therapy with other innovative therapeutic methods, such as chemotherapy, immunotherapy, and gene therapy. The use of appropriate modifications not only increases the therapeutic effectiveness but also prevents damage to healthy cells and tissues. The studies described clearly demonstrate the great efficiency of polymer-functionalized nanoparticles in killing cancer cells. Some recent studies, however, have shown that photothermal therapy is always accompanied by a heat shock response. This effect shields cancer cells from hyperthermia damage, consequently decreasing its therapeutic efficacy. Usually, to increase therapeutic efficacy, a larger administration dose or higher irradiation power is necessary, causing severe side effects due to the overheating of neighboring normal tissues. The use of gene therapy combined with phototherapy is a fascinating candidate for solving this problem. Killing cancer cells without inducing cellular thermoresistance by photothermal therapy is one of the biggest challenges in this field.

4. POLYMER MATRIX COMPOSITES

Polymer matrix composites are materials formed from at least two different types of components, e.g. polymer matrix and ceramic/metal nanofillers.[94] In these materials, the polymer matrix is a hosting network, and nanofillers are the photothermal agents. The objective of composite development is to create new materials that will combine the advantages of both components

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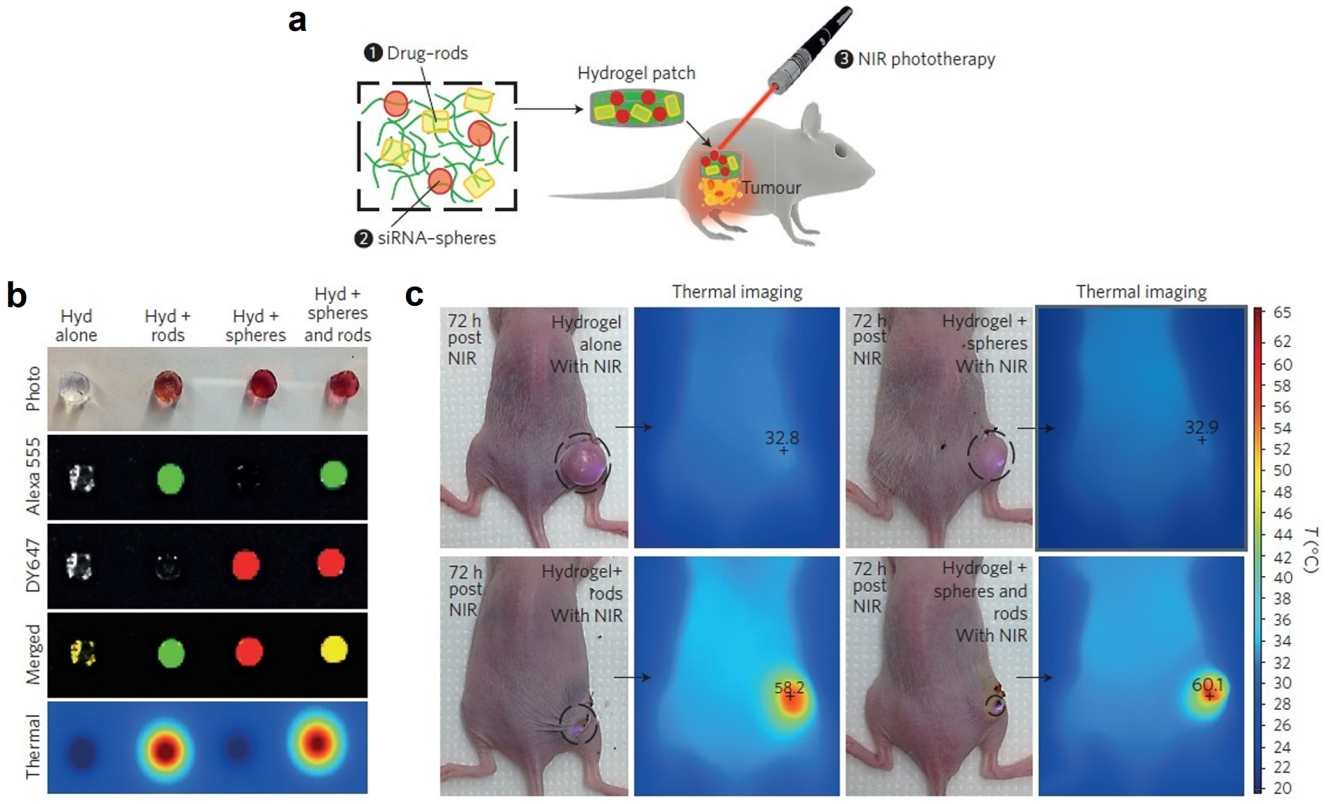

Figure 9. (a) Schematic of the smart hydrogel−nanoparticle patch with drug−siRNA nanoparticle conjugates (drug−gold nanorods and siRNA−gold nanospheres) for local gene and drug release designed by Conde et al.[99] (b) Fluorescence and thermographic images of hydrogel patches. (c) Thermographic surveillance of the photothermal heating of hydrogel patches in mice (*n*D5) 72 h after the first NIR treatment. Reprinted by permission from Springer Nature, ref 99. Copyright 2016, Macmillan Publishers Limited. http://www.nature.com/nmat/.

at the same time. As of today, the latest trend in cancer treatment is the development of techniques based on a combination of various treatment methods (e.g., combined chemo- and photothermal therapy) that operate locally. Local treatments make it possible to maximize the bioactive molecule concentration in the cancer area while minimizing the drug toxicity of other tissues. This type of treatment has been considered much more effective than conventional chemotherapy.[95]

Various delivery systems such as drug-loaded fibers or hydrogels have been studied for local therapy in recent years.[96,97] As we have already pointed out, however, a single cancer treatment method is not sufficient because of both inefficient drug permeability at the cancer site and the drug resistance of tumor cells.[98] Therefore, thermally responsive polymer matrix composites are a promising solution because they can easily host drugs and photothermally active particles. Moreover, because of the polymer responsivity, the final material can be used as an on−off switch for drug release under NIR irradiation.[99] In the case of drug release, the hyperthermia effect of photothermal therapy not only kills cancer cells but also increases drug penetration into the tumor site.[100,101] In this case, side effects caused by nontarget accumulation occur together with an unsatisfactory anticancer efficiency.[100] However, drug release is still not an entirely controllable process. Furthermore, additional advantages of the use of polymers in biomedical applications stem from the biodegradable nature of these materials.[102]

The properties of polymer composites (e.g., mechanical properties, degradation rate, and drug release) are highly dependent on structural morphology at the molecular level, such as crystallinity fraction or crystallite size, and polymer chain structure. It is worth remembering that polymer structure is characterized by temperature-dependent features. When surface plasmon resonance (SPR) is induced in the polymer composite, due to the inclusion of inorganic nanofillers, energy is transferred from the particle to the surrounding polymer matrix, causing local polymer melting and consequently leading to changes in its structure.[94,103−105] The effect of photothermal heating on the polymeric structure has been extensively described by Viswanath et al.[103] They demonstrated that a low annealing temperature reached during the photothermal process led to the maximum polymer crystallinity in a shorter annealing time than with conventional annealing procedures (Figure 8). Gold nanoparticles embedded into polymer matrixes are localized heat sources that make it possible to manipulate crystallinity, cross-linking, and chemical reactions. Using this nature-inspired cascade approach, the internal structure of polymer matrix composites can be altered at any point in their life cycle by photothermal treatments. Indeed, light responses can act as mediator signals that generate material structural transformations and in turn offer additional functionalities (e.g., on−off release of bioactive molecules) to the material.[99,102,106]

Today, there are only a few scientific papers devoted to polymer matrix composites. They are briefly described next.

4.1. Hydrogels. Hydrogels are three-dimensional constructs formed by hydrophilic polymers in which the polymer chains are cross-linked physically or chemically to form a network. The capability to accumulate large amounts of water is a characteristic feature for hydrogels, which may reach up to 90% of their

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bulk mass. High water content, softness, flexibility, and biocompatibility make hydrogels very similar to natural tissues. At the same time, this type of material has certain limitations, e.g., toxic cross-linking agents that may remain in the bulk, inhomogeneity of nanoparticle dispersion, or poor mechanical properties.[107] Moreover, a few hydrogels are responsive to different kinds of environmental condition changes, like pH or temperature. Thermosensitive hydrogels are characterized by lower and upper critical solution temperatures (LCST, UCST), which indicate the temperature points of hydrogel state transitions. Some hydrogels formed for controlled drug release show a LCST slightly above body temperature. When the temperature of the copolymer exceeds the LCST, the hydrogel collapses and releases any components suspended in the hydrogel matrix.[107−109] Hydrogels are currently used for manufacturing various medical devices, such as contact lenses, tissue engineering scaffolds, drug delivery systems, and wound dressings.[107] The application of this type of material for photothermal cancer therapy was recently explored by several scientists.[99,110−112]

Hydrogel materials for cancer therapy have been developed and studied by Conde et al.[99] These authors proposed the use of one single hydrogel patch capable of combining gene, drug, and photothermal therapies all at the same time. This hydrogel contains nanofillers such as gold nanorods and gold nanospheres. Nanorods have been functionalized with appropriate biomarkers to enhance their uptake by cancer cells. These biomarkers made it possible to eliminate the problem connected with absorption by healthy cells and the strong hypothermia impact on them. Using confocal microscopy and proper labeling techniques, the authors proved that nanoparticles are more effectively absorbed by CRC cells (cancer cells) than 3T3 fibroblasts. MTT assay also confirmed the decreased tumorgenicity of CRC cells after laser irradiation. The hydrogel formed using poly(amidoamine) and the above-mentioned particles were analyzed in in vivo tests using mouse models (Figure 9). It has been shown that the designed hydrogel nanocomposite is a good material for nanoparticle and drug delivery into cancers as well as an effective carrier for the quick diffusion of therapeutic agents into cancer cells. However, some questions concerning implantation procedure (e.g., depth, insertion, and fixation) still remain under debate. Moreover, the rapid changes in the material structure and its consequent possible damage after reaching the LCST point, which facilitates the quick release of drugs, remains an unsolved problem.

For the implantation of hydrogel composites to be improved, injectable materials should be taken into consideration. Xing et al. have described an injectable, self-healing hydrogel with self-assembly biomacromolecules.[110] In this study, natural polymers such as collagen, elastin, and silk fibroin were used. The interactions between polymer gelators and nanoparticles have been used to assemble tunable and self-healing polymeric materials. Additionally, nanoparticles play a key role in tuning mechanical properties, and the polymeric matrix remains a good environment for water-soluble drug diffusion. The authors extensively described the healing mechanism of this hydrogel, focusing on the gold nanoparticle−collagen interaction. It was proven that intratumoral-injected hydrogels could be sustained in situ and that the drugs were successfully released.

A few studies reported that the process of selective treatment of cancer cells by hyperthermia needs to be improved.[111] The hydrogel composite formed with spinach extract, reduced graphene oxide, gold nanocages (AuNCs), and fluorouracil (5-FU) effectively increased the temperature and released the drug, leading to successful reduction of HeLa cell proliferation. However, CHO cells, used as a control, were also shown to exhibit reduced proliferation. This effect is due to the rGO and/or AuNC release, which additionally affects CHO cell proliferation. The authors, however, only presented profiles for 5-FU without showing data for rGO or AuNC release.[111] In this case, the effectiveness and targeting ability of the active compound could be modified by appropriate biomarkers as proposed by Conde et al.[99]

For hydrogels, as well as for any other type of 3D material, implantation remains a crucial problem. A good idea for the proper placement of hydrogel composite components is in situ cross-linking. Zhang et al. explored this type of strategy with a idea of synthesizing a novel hydrogel for synergistic cancer therapy.[113] The hydrogel was formed by poly(ethylene glycol) double acrylates (PEGDA) and a titanium dioxide/multiwall carbon nanotube (TiO_2@MWCNT) nanocomposite, which acts as a photoinitiator and photothermal agent for cancer multimechanism therapy, and DOX applied as a model drug. The proposed material showed a certain recyclability, which may be important for successful treatment and long-lasting drug release. However, the reported data also showed that limited UV or NIR light penetration may be an additional problem. For these reasons, this material may not be suitable for deeply located tissue treatments.[114,115]

An injectable drug delivery system that provides photothermal transduction activity was proposed by Zhou et al.[116] The developed system contains single-wall carbon nanotubes (SWNTs), PNIPAM hydrogel, and doxorubicin. The combination of hyperthermia therapy and controlled DOX release gave a higher cancer suppression rate on gastric cancer xenograft mouse models than did free DOX, and no organ toxicity was detected. However, the application of rGO or carbon nanotubes in medical treatments seems to be yet uncertain. The release profiles, accumulation in tissues, and cytotoxicity are constantly studied and yet are still unclear.[117,118]

Polymer matrix composites in the form of hydrogels may be successfully used as medical materials for combined cancer therapy (chemo- and photothermal therapy). Some problems concerning the nature of these materials should also be solved. Furthermore, the accurate control of the heating under NIR irradiation to avoid damaging the hydrogel structure and fast drug release will be the biggest challenges in this field.

4.2. Fibrous Membranes. Polymer membranes already play a significant role in fields such as water purification, fuel cells, cell scaffolds, and wound dressings. Membranes may be formed by various techniques, e.g., melt electrospinning[119] or electrospinning,[120−124] solvent casting and particle leaching,[125] or freeze-drying.[126] In the case of polymer matrix composites for photothermal cancer therapy, however, just a few of these have been investigated. Nonwovens can be fabricated by various techniques, thus making it possible to obtain fibers with diameters ranging from dozens of nanometers to a few micrometers.[120−124] Fibrous nanomaterials are promising materials for medical applications such as photothermal cancer therapy due to their highly active surface area to which drugs or particles can be attached.

The concept of using fibers for photothermal therapy is quite new, and only a few papers have been published recently on this subject. Zhang et al. proposed poly-L-lactic acid (PLLA) composite nanofibers loaded with multiwalled carbon nanotubes (MWCTs) and doxorubicin.[102] Moreover, in this

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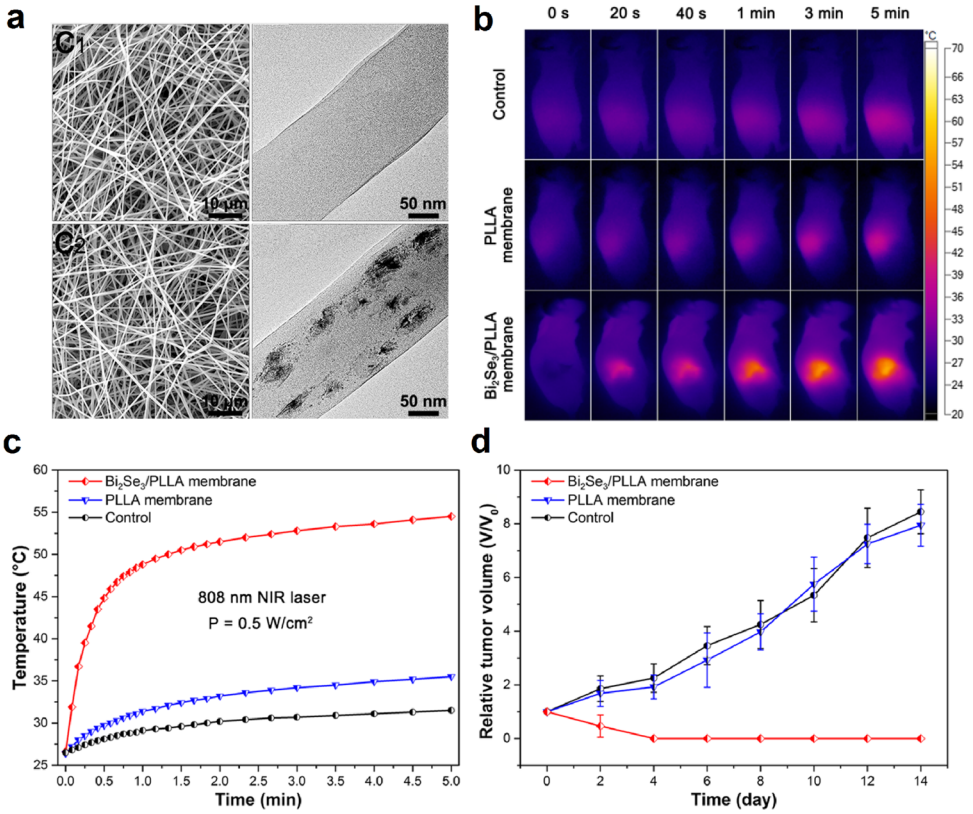

Figure 10. (a) Scanning electron microscope (SEM) and transmission electron microscopy (TEM) images of PLLA and Bi_2Se_3/PLLA membranes. (b) Infrared thermographic maps and time-dependent temperature increase in the tumor-bearing nude mice irradiated by an 808 nm laser. (c) Temperature growth during the irradiation of PLLA and Bi_2Se_3/PLLA membranes. (d) Corresponding growth curves of tumors in different groups of mice after NIR laser irradiation. Reprinted with permission from ref 127. Copyright 2017, American Chemical Society.

scientific work, polytherapy (chemo- and photothermal therapy) has been suggested for cancer treatment, and the on−off switching mechanism of drug release was described. PLLA has a low glass-transition temperature (T_g) of ∼60 °C. Because human body temperature is under the T_g of PLLA, the as-prepared material is in its glassy state, and the polymer chain mobility is limited. Therefore, the release of DOX from the fibers is rather slow (5−8% per 12 h, depending on pH). After irradiation, however, a great deal of heat is efficiently generated by MWCNTs. When the temperature exceeded the PLLA T_g, the mobility of the polymer chain increased, enhancing the drug release (20% per 2 h after 30 min of irradiation). This work proved that nanofibers can effectively combine two cancer treatment methods to deliver drugs effectively and locally. This material can be easily used for the treatment of skin cancer, but its implantability remains uncertain. Furthermore, as was described in the previous paragraph, the problem connected with the MWCNT cytotoxicity is still unsolved.

Nonwovens for photothermal therapy were also analyzed by Shao et al.[127] Locally produced energy was an effect of bismuth selenide (Bi_2Se_3) irradiation. In this work, Bi_2Se_3 nanoplates were incorporated into the poly(lactide) fiber matrix and tested as photothermal agents (Figure 10).

The authors showed that composite fibers effectively increase the temperature of the medium while killing HeLa cancer cells. In this case, however, one important issue should be further taken into consideration: the authors did not present data concerning bismuth selenide release from fibers before and after irradiation nor on its cytotoxicity for noncancer cells. If such a significant temperature increase appears during irradiation, PLLA molecule mobility is increased, and nanoplates may be easily released to the environment.[128] This problem is not visible when analyzing monocultures of HeLa cells because target cells are logically successfully killed. However, in co-culture, such as under in vivo conditions, both healthy and cancer cells coexist. In this case, it is hard to say if either only local hypothermia is responsible for cell death or if the cytotoxicity of bismuth selenide is also a cause of it.[127] The concept of selectively attaching biomarkers could be used in this case, as was done by Conde et al.[99] to limit bismuth selenide effects on healthy cells.

Additionally, nanofibers may be surface-functionalized to introduce bioactive components for treatment purposes.[129] However, the attached substances should be carefully selected to avoid inducing cytotoxic effects.[118] Moreover, it should be remembered that surface-functionalized fibers show very different particle/drug release kinetics and photothermal effect efficiencies than do bulk-loaded fibers.

Various technologies are available today to fabricate fibers on a mass scale. Most of them use polymer solutions or melted polymers. This may be problematic if biologically active molecules for combined therapy are to be added to fibers. Aggressive solvents or high temperature could cause the degradation of these components. To summarize, the implantation procedure of nonwovens, their degradation under in vivo conditions, and the influence of solvent traces should be further investigated.

Only a few scientific articles on polymer nanocomposite membranes with different morphologies for photothermal therapy have been published recently.[130−132] Li et al. fabricated polydimethysiloxane (PDMS) membranes containing gold

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nanoparticles that were synthesized by the in situ method.[130] In the case of composite membranes with nanoparticles, potential segregation of components may occur, thus leading to a higher intensity of the NIR radiation needed for photothermal effects. To avoid this problem, Li et al. decided to use in situ polymerization. Wet and dry samples of the proposed composites were studied. It has been demonstrated that the amount of remaining solvent traces affects the intensity of the photothermal effects. Upon laser irradiation, wet membranes reached lower temperatures than dry membranes. The authors explained that, most likely, the heat generated by gold nanoparticles is dissipated throughout the entire system (both the remaining solvent and the polymer matrix) in wet membranes, resulting in a lower temperature of these materials compared to that of dry membranes.[131,132] The data presented may help to understand the differences in the efficiency of photothermal effects in the previously mentioned hydrogels or nonwoven materials.

To date, various forms of polymer matrix composites for photothermal cancer treatment have been investigated. As can be seen, all of them show significant advantages, i.e., are good vehicles for drugs and nanoparticles and induce localized hyperthermia, but they also have a few disadvantages, including not fully controlled drug release and a limited implantation localization and depth. Despite this, polymer matrix composites are the most promising materials for the development of functional materials for the combined chemo- and photothermal therapy of cancer.

5. NEW TRENDS

In the fight against cancer, compared with traditional therapeutic approaches (e.g., chemotherapy, radiotherapy, and immunotherapy), PTT exhibits very unique advantages such as selective targeting and minimal invasiveness. PTT has the capability to destroy cancer cells in the primary tumor (mainly if localized in superficial tissues) and to combat the initial stage of cancer metastasis. Moreover, PTT can effectively destroy cancer stem cells and tumor initiating cells, avoiding metastatic propagation to distant organs. It is important to say that PTT can kill cancer cells via cellular necrosis, enabling an inflammatory response that can affect the efficacy of the same treatment. For this issue to be overcome, it has been demonstrated that it is the possible to trigger the PTT heat in such a way to induce apoptosis (which does not generate an inflammatory process) rather than necrosis.[10] On the other hand, at the current stage, PTT fails if applied after the metastatic process has taken place, such as in the presence of aggressive tumors involving important organs or tissues that are already far away from the primary tumor. For this issue to be overcome, novel nanoplatforms able to efficiently combine PTT with other therapies to exert a stronger impact in the presence of metastasis have been combined. In this framework, photo-responsive nanoagents have been exploited for combined PTT-immunotherapy.[133] The results have shown that nanotube-based PTT could modulate the adaptive immune responses for the treatment of metastatic cancers. PTT agents could not only be used for photothermal tumor destruction but also act as immunological adjuvants promoting the maturation of dendritic cells and production of antitumor cytokines. These data prove that, after photothermal ablation of the primary tumor, the induced immunological responses are able to inhibit secondary tumors as well as lung metastasis. Another approach is based on the fact that cellular dysfunction due to radiation is mediated by microvascular endothelial damage and that, therefore, chemical vascular-disrupting agents could be effective in combination with radiation therapy for tumor vascular disruption. These agents are promising materials for improving therapeutic outcome and their applicability can be extended to tumors that barely respond to standard therapies. Kunjachan et al. proposed a dual-targeting strategy to improve tumor blood vasculature radiation outcome by inducing vascular damage.[134] This study experimentally validated the hypothesis that tumor-specific vascular disruption could be mediated by the administration of targeted nanoparticles followed irradiation, which could be easily extended to PTT nanoplatforms.

The development of novel nanomaterials for photothermal therapies is evolving rapidly. Current strategies concern not only monotherapies but also NIR-controlled heating of cancerous cells with, for example, gold nanorod nanoparticles. These novel advanced medical treatments require the development of combined therapies using NIR illumination for inducing chemotherapeutic drug release or photodynamic therapy. One of the emerging techniques used for the formation of multifunctional biomaterials is electrospinning. In this method, a polymer solution is stretched by electrostatic forces that develop between a needle connected to a high voltage supply and a grounded collector to form ultrathin fibers. Moreover, because of the nanosized fiber diameter, the developed materials show structural similarity to the naturally produced proteins and polysaccharide complexes present in the extracellular matrix (ECM), positively influencing cellular proliferation and activity.[121] As we will show in this paragraph, electrospinning can combine all the properties of the above-mentioned materials: conjugated polymers can be electrospun while the electrospun nanomaterial surface can be easily functionalized, and it is even possible to fabricate composite nanomaterials to develop novel heat-generating devices. One of the best examples of this is the development of $CaTiO_3$:Yb,Er nanofibers coconjugated with Rose Bengal (RB) and gold nanorods.[135] The incorporated RB served as the photodynamic therapy agent, and the gold nanorods attached to the nanofiber surface were responsible for the hyperthermia effect. Additionally, upconversion photoluminescence (UCPL) of $CaTiO_3$:Yb,Er nanofibers was used to excite RB and gold nanorods so that photodynamic and photothermal therapy could occur simultaneously during irradiation with a laser source (λ = 980 nm) with deeper tissue penetration. The combination of several treatments is particularly significant due to the resulting synergistic effect that shrinks the tumors and stops the metastatic spread of cancer, in which cells escape from the primary tumor and form new ones. Moreover, every monotherapy has its own side effects; therefore, combining different therapeutic approaches can help eliminate heterogeneous cancer cells that cannot be treated with single chemotherapeutic agents due to drug resistance.

The rise of new strategies in the treatment of tumors is essential for the complete eradication of cancer cells from the body. PTT is a promising method for increasing temperature to a level that induces the apoptosis of cancer cells via localized hyperthermia; on the other hand, this method also makes it possible to trigger other processes that could also help eliminate cancer cells. One of these methods is the on−off release of drugs. For instance, Park et al. have described an experiment in which fibrous polycaprolactone (PCL) materials containing phase-changeable fatty acids and indocyanine green were illuminated with NIR light.[136] Upon NIR illumination, the temperature of the material increased above the melting point of the fatty acids,

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thus causing greater drug release from the material. This strategy could limit the harmful impact of chemotherapeutic drugs, being more beneficial for patients' health. Another interesting functionality that could help clinicians in assessing the response to treatment is the monitoring of the drug release from the implanted biomaterial itself.[137] The incorporation of Yb^{3+}/Er^{3+} into $CaTiO_3$ nanofibers helped control the release of doxorubicin; additionally, the amount of this kind of bioactive molecule could be easily assessed optically by evaluating the intensity ratio of green to red emissions of UCPL nanofibers under irradiation with a 980 nm laser. Another innovative strategy is the simultaneous capture and killing of cancer cells described by Mauro et al.[138] They have functionalized the surface of PCL fibers with graphene oxide. This allowed the selective capture of circulating tumor cells, and upon irradiation of NIR light, the temperature increase eradicated them photothermally. This is a potential tool not only for eliminating metastatic cells but also for the early detection of cancer cells thanks to the fluorescence properties of this material. In any case, although the idea of capturing and eradicating circulating tumor cells with NIR light is promising, the long-term consequences of using graphene oxide in implantable nanomaterials are not well-known. The above-mentioned hybrid scaffold could be implanted under the patient's skin, thus making it more accessible for NIR light illumination. However, new PTT agents are necessary for treating inaccessible tumors with light in the NIR I region.

As mentioned in the previous paragraph, numerous photothermal agents, especially nanomaterials with strong absorbance in the tissue-transparent NIR I (650−950 nm) region, have been studied extensively for use in PTT. The low penetration depth of laser light is one of the limiting factors that permit treating superficial cancers only, such as skin and breast tumors. The illumination of tissues by lasers operating in the NIR II window (950−1700 nm) offers a higher light penetration depth. One of the most fascinating examples of this is the use of $CaTiO_3$:Yb,Er nanofibers, which, thanks to UCPL, emit light-activating photosensitizers and heat-generating agents, leading to a synergistic effect of photodynamic and photothermal therapies when irradiated with a 980 nm laser.[135,137] Nanomaterials filled with nanoagents that absorb light in the NIR II region have a high aspect ratio, and the upconversion photoluminescence present could potentially be used for the formation of theranostic medical devices, opening new possibilities for the simultaneous diagnosis and efficient treatment of tumors.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

From the very beginning, inspiration from nature has proven to be very helpful for the development of advanced materials with novel and unpredictable properties, looking at the mechanisms involved in life processes as they occur in nature but with an in-depth knowledge of material sciences. Proper design and application of theranostic biomaterials based on polymer PTT agents require a deep understanding of the features that distinguish them from other smart materials. Polymer-based PTT nanoplatforms offer many advantages, such as ease of fabrication, biocompatibility, and especially the possibility to tune their cascaded responsive properties to trigger other local cancer treatments such as chemo-, gene-, or photodynamic therapy.

This review provides an overview on the progress made toward the production of different types of polymer-based multifunctional nanomaterials for PTT. Three main material classes have been identified: conjugated polymer nanomaterials, polymer-functionalized nanoparticles, and polymer matrix composites. All of them are composed of different types of polymers, and the processes used in responding to light stimulation in a controlled cascade-like fashion are based on different mechanisms; therefore, every described class presents specific advantages and shortcomings.

In summary, conjugated polymers are highly versatile materials that can be synthesized through well-established reactions (e.g., click chemistry, copolymerization, ester-coupling, and polycondensation). Moreover, they can be functionalized after polymerization to introduce novel functional groups. This makes these polymers ideal building blocks for materials with enhanced light-to-heat conversion (e.g., improving the light-harvesting ability in the second NIR window). Additionally, conjugated polymers such as polythiophene derivatives can be easily modified to increase their water solubility. Conjugated polymers can be modified to finally form copolymers with D−A properties, and they can be combined with wide-absorption organic dyes to further increase their photothermal conversion efficiency. Conjugated polymers in the form of nanoparticles can help control the drug release process; they can also improve the treatment efficacy and, at the same time, could minimize the side effects of, for example, chemotherapies. Moreover, nanoparticles, in addition to transporting a drug cargo, can also be bound to target cells and generate signals for imaging purposes as well as generating ROS to perform PTT and PDT simultaneously. However, several challenges need to be addressed before these nanosystems can find a clinical application: low photothermal conversion efficiency and low photostability in vivo, for instance. Another issue is the fast renal clearance of nanomaterials and their overaccumulation in nontargeted tissues, which may trigger additional serious side effects. Therefore, we can conclude that platforms based on conjugated polymers have shown outstanding light−material interaction properties as well as exceptional multifunctional performance, but the interaction of these materials with body tissues should be the subject of further investigations before they can be considered as biomaterials suitable for potential applicability to clinical oncology.

The surface functionalization of PTT nanoparticles by polymers was initially explored to stabilize nanomaterials and to increase their biocompatibility, prolonging their circulation within the body and avoiding the direct contact of body tissues with the metal or inorganic surface of the particles. Recently, nanoparticle capping by biomolecules such as peptides or nucleic acids was used to create multifunctional platforms able to combine PTT with other advanced cancer therapies (e.g., gene therapy) activated by the interaction of the nanomaterials with NIR radiation. This intriguing methodology created new opportunities in the biomedical field. However, it is worth pointing out that the presence of functional polymer layers around PTT nanoagents does not allow a significant improvement of the efficiency of the photothermal effect because it is mainly driven by the core features.

Polymer matrix composites are the last class of nanomaterials that has been explored in this well-detailed overview. These materials have been investigated in depth only in the past decade, but their scientific interest is growing quickly because of the possibility to combine the advantages of both aforementioned material classes. Therefore, in this case it is possible to improve both light−material interaction and biocompatibility as

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well as obtain several new functionalities driven by the polymer matrix modification (e.g., crystallinity) that occurred during heat generation. Noteworthy, PTT hydrogel-based nanoplatforms, because of their intrinsic high water content, softness, and flexibility (very similar to natural tissues), have great potential for the development of fully biocompatible multi-stimuli-responsive and versatile theranostic nanomedicine platforms. Most importantly, polymer composites can be easily processed by electrospinning to form nanofibrous platforms, paving the way for the development of tissue-engineered scaffolds and localized smart drug delivery systems, which is the most valuable perspective in the field. Today, the incorporation of drugs with photothermally active agents in the polymer nanofiber matrix leads to distinct and synergistic chemo-photothermal therapies while at the same time providing an ideal environment for tissue regeneration after cancer removal. The use of nanocomposites for this purpose is still in the initial stages; therefore, accurate pharmacokinetics and pharmacodynamics data are still unavailable. Consequently, systematic and rigorous in vivo evaluations, especially regarding the degradability, toxicity, and long-term side effects of nanomaterials, are needed, but they have not yet been thoroughly performed because of the complexity of the processes of nanomaterial biodistribution and elimination from the body.

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Notes

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ABBREVIATIONS

WHO, World Health Organization; PTT, photothermal therapy; NIT, near-infrared; CPs, conjugated polymers; PA, photoacoustic; PDT, photodynamic therapy; ROS, reactive oxygen species; ED, electron-rich; EA, electron-deficient; NPs, nanoparticles; PT, photothermal; PD, photodynamic; PANI, polyaniline; EB, emeraldine base; ES, emeraldine salt; PNIPAM, poly(*N*-isopropylacrylamide); dPG, dendritic polyglycerol; DBSA, *n*-dodecylbenzenesulfonic acid; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; FA, folic acid; DOX, doxorubicin; PPy, polypyrrole; Astx, astaxanthin; BSA, bovine serum albumin; DSPE-PEG2000, 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)-2000]; PTh, polythiophene; ICG, indocyanine green; OSCC, oral squamous cell carcinoma; CPNs, conjugated polymer nanoparticles; DPPV, poly{2,2′-[(2,5-bis(2-hexyldecyl)-3,6-dioxo-2,3,5,6-tetrahydropyrrolo[3,4-*c*]pyrrole-1,4-diyl)-dithiophene]-5,5′-diyl-*alt*-vinylene}; PtTFPP, Pt(II)-meso-tetra(pentafluorophenyl)porphyrine; PFO, poly(9,9-di-*n*-octylfluorenyl-2,7-diyl); PFBT, poly[(9,9-dioctylflurenyl-2,7-diyl)-*co*-(1,4-benzo-{2,1′,3}-thiadiazole)]; TPP, tetraphenylporphyrin; Cy, Cyanine; CyP, poly(heptamethine) Cy-containing derivative; BTPBF, bis(5-oxothieno[3,2-*b*]pyrrole-6-ylidene)-benzodifurandione; BT, 3,3′-didodecyl-2,2′-bithiophene; cRGD, cyclic arginine-glycine-aspartic acid; PFVBT, poly[9,9-bis(2-(2-(2-methoxyethoxy) ethoxy)-ethyl) fluorenyldivinylene]-*alt*-4,7-(2,1,3-benzothiadiazole); PIDTTTQ, poly-[(4,4,9,9-tetrakis(4-(octyloxy)phenyl)-4,9-dihydros-indacenol-dithiophene-2,7-diyl)-*alt*-co-4,9-bis(thiophen-2-yl)-6,7-bis(4-(hexyloxy)phenyl)-thiadiazolo-quinoxaline]; TBDOPV, thiophene-fused benzodifurandione-based oligo(*p*-phenylenevinylene); DT, 2,2′-bithiophene; BBT-2FT, benzo[1,2-*c*;4,5-*c*′]bis-[1,2,5]thiadiazole-4,7-bis(9,9-dioctyl-9H-fluoren-2-yl)-thiophene; BBT, benzo-bis-thiadiazole; BIBDF, bis(2-oxoindolin-3-ylidene)-benzodifuran-dione; BT, bithiophene; BDT-IID, 4,8-bis[5-(2-ethylhexyl)thiophen-2-yl]-2,6-bis-(trimethylstannyl)benzo[1,2-*b*:4,5-*b*′]dithiophene-6,6′-dibromo-*N*,*N*′-(2-ethylhexyl)isoindigo; PSMA, poly(styrene-*co*-maleic anhydride); Pdot, polymer dot; DPP-DT, diketopyrrolopyrrole-dithiophene; PF-DBT5, poly[(9,9-dioctylflurenyl-2,7-diyl)-*co*-(4,7-di-2-thienyl-2,1,3-benzothiadiazole)]; PBdots, polymeric blend dots; PFDHTBT, (poly[(9,9-dioctylflurenyl-2,7-diyl)-*co*-(4,7-bis(4-hexylthiophen-2-yl)-2,1,3-benzothiadiazole)]; PEG, poly(ethylene glycol); Chit-AgNTs, chitosan-coated silver nanotriangles; CMCS, *O*-carboxymethyl chitosan; HepG2, hepatocellular carcinoma cell line; pHLIP, pH Low Insertion Peptide; rGO, reduced graphene oxide; LGNPs, lycosin-I-conjugated spherical gold nanoparticles; LGNRs, lycosin-I-modified gold nanorods; GNRs, gold nanorods; PGNRs, peptide-modified gold nanorods; siRNA, small interfering RNA; PSS, poly(sodium 4-styrenesulfonate); PDDAC, poly(diallyldimethylammonium chloride); PC-GNRs, gold nanorods modified by phosphatidylcholine; Apt@Au NPs, aptamer-functionalized gold nanoparticles; Apt@Au NRs, aptamer-functionalized gold nanorods; PEO, poly(ethylene oxide); LCST, lower critical solution temperature; UCST, upper critical solution temperature; AuNCs, gold nanocages; 5-FU, fluorouracil; PEGDA, poly(ethylene glycol) double acrylates; TiO_2@MWCNT, titanium dioxide/multiwall carbon nanotube; SWNTs, single wall carbon nanotubes; PLLA, poly-L-lactic acid; MWCTs, multiwalled carbon nanotubes; T_g, glass transition temperature; Bi_2Se_3, bismuth selenide; SEM, scanning electron microscope; TEM, transmission electron microscopy; PDMS, polydimethysiloxane; ECM, extracellular matrix; RB, Rose Bengal; UCPL, upconversion photoluminescence; PCL, polycaprolactone.

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