Review Article

Therapeutic Nanomaterials for Neurological Diseases and Cancer Therapy

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Received 11 April 2020; Accepted 3 August 2020; Published 25 September 2020

Guest Editor: Garima Agrawal

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In the recent decade, nanomedicine and nanotechnology have been broadly developed leading to a significant advancement in biomedical research as well as clinical practices. The application of several functionalized nanomaterials on the molecular and cellular levels has yielded a lot of promising progresses in various fields of regenerative medicine including disease diagnosis, combinational cell therapy, tissue engineering, and drug and gene delivery. In this review, we will summarize the recent approaches of nanoscale materials utilized in neurological diseases and cancer therapy, with highlights on the most current findings and future prospects of diverse biomedical nanomaterials for tissue regeneration, drug innovations, and the synthesis of delivery system.

1. Introduction

Nanomedicine is a promising field that uses nanosized (10–100 nm) materials to facilitate the diagnosis and treatment of diseases. These nanomaterials with being used as a drug are also used as a carrier, a scaffold, or an imaging agent [1–3]. In common, all these applications could benefit from the extraordinary properties of nanomaterials, such as high specific surface area, transformable shape and size, and tunable chemical reactivity. A high surface area gives nanomaterials a huge adsorption capacity to load various molecules of a certain density like drugs, proteins, genes, and metal ion for the drug delivery, targeting ability, or disease interventions. In addition, shape (sphere, rod, wire, fiber, tube, etc.) and size can also influence the characteristics of nanomaterials [4, 5]. All these clues indicate that nanomaterials

possess an ever-changing capacity, enabling them to adapt to different application environments.

Neurological diseases and cancer are affecting approximately billions of people worldwide irrespective of age, sex, education, or income. Neurological diseases, including Alzheimer's (AD), Parkinson's (PD), and stroke, have caused tremendous pressure on human health. Not only is the pathogenic mechanism still unclear, the special anatomical location of the brain and its criticality also make few drugs safe to achieve therapeutic effects. The blood-brain barrier (BBB) is obviously one of the key barriers. It prevents most drugs from freely entering and leaving the brain, but its integrity is vital to the safety of the central nervous system. Therefore, we can only try to bypass or cross this barrier in certain ways without destroying the BBB. Drugs based on nanomaterials are one of the promising ways to realize this idea. In

addition, specially designed nanomaterials can also improve the thrombolytic process of ischemic stroke and the effect of stem cell transplantation. Similarly, in cancer treatment, nanomaterials rely on their unique advantages to accurately target some biotoxic drugs to cancer tissues without causing damage to normal tissues [6].

Currently, a wide variety of nanomaterials have been tested in neurological diseases and tumors, including liposomes, micelles, polymeric nanomaterials, carbon nanotubes, quantum dots, and metallic nanomaterials. Each of them shows great promise in clinical applications, although there are still many shortcomings to be resolved. Several nanomaterials, including liposomal vincristine, liposomal irinotecan, PEGylated IFN beta-1a, and PEGylated factor VIII, have been approved by the US FDA, or in the FDA clinical trial processes [7] which signify the development of nanomaterials and their journey from lab to bedside. In this review, we will focus on the application of nanomedicine in neurological diseases and cancer.

2. Therapeutic Nanomaterials for Neurological Diseases

2.1. Nanomaterial for Neurodegeneration. Neurodegenerative diseases such as Alzheimer's (AD), Parkinson's (PD), and amyotrophic lateral sclerosis (ALS) generally have a long pathological damage process, which causes inestimable harm to the patients and their families [8]. Since the 1990s, with the continuous maturity of nanotechnology, the technical barriers to nanomaterial research have disappeared [9]. In the studies of neurodegenerative diseases, nanomaterials have gradually entered the field of vision for researchers. Various nanomaterials including lipid-based nanomaterials (liposomes, solid lipid nanoparticle (SLN)), polymeric nanomaterials (micelle, dendrimer, nanocapsule, and nanosphere), and inorganic nanomaterials have been used for research.

At present, the research direction of nanomaterials in neurodegenerative diseases is mainly focused on drug delivery, maintaining drug concentration, and early accurate diagnosis and treatment of diseases based on the characteristics of nanomaterials. For example, lipid-based nanomaterials and polymeric nanomaterials showed great biocompatibility and membrane penetrating power [10, 11]. They have significant advantages over traditional drugs in their ability to cross the blood-brain barrier (BBB), along with the slow and controlled release of the drug. In the research of PD, the use of poly lactide-co-glycolide (PLGA) as a controlled release shell for levodopa or neurotrophic factors has been studied by researchers for more than 20 years [12–14]. Gold nanomaterials, carbon nanotubes, and other inorganic nanomaterials are easy to shape and transform and can be stably identified by imaging and laboratory methods. An interesting study published in 2017 pointed out that the BBB permeability of gold nanomaterials is closely related to their shape; the size with 20 nm circular particles could achieve the strongest penetration [15]. Nowadays, with the development of imaging science, various studies on the enhancement of imaging performance of gold nanomaterials have emerged endlessly. Some research groups demonstrated that dopamine could

enhance Raman spectroscopic scattering on the surface of self-assembled gold nanomaterials, making it possible to monitor dopamine levels in the brain [16]. The applications of various nanomaterials in the treatment of neurodegenerative diseases were exhibited in Table 1 [17].

2.2. Nanomaterials for Neuroprotection. Stroke is the leading cause of death and disability around the world [49–51]. 87% of cases are ischemic stroke, caused by cerebral vascular embolism. However, there are no more effective treatments in clinical practice, except for tissue plasminogen activator-(tPA-) mediated thrombolytic or mechanical thrombectomy within the prescribed time [52, 53]. Currently, nanomaterials are considered to have great potential in the field of stroke treatment [54, 55]. Three research directions attract the most attention: (i) construction of safer and more efficient tPA-coated nanomaterials, (ii) antioxidants delivered through nanomaterials to reduce reperfusion injury, and (iii) generation of neuroprotective nanoscale exosomes.

Novel tPA-coated nanomaterials have been reported multiple times in the thrombolysis studies. Various kinds of structures and materials were applied in such researches. Shear- [56, 57], sound- [58–61], light- [62], and magnetic- [63, 64] sensitive nanomaterials were designed to improve the thrombolytic efficiency of tPA and reduce its side effect by changing the external physical environment. A previous study in our lab demonstrated that nickel-nanorod-composed nanomotors could be used as an independent input to strengthen the efficacy of tPA in a mouse embolism model [63]. Later on, we synthesized tPA-coated Fe₃O₄ nanorods, which could be accurately targeted at the thrombus site under the guidance of a magnetic field. Fascinatingly, a mechanically rotated force could be created in an external rotational magnetic field, which not only provides physical strength to break down the clot but also allows more tPA to be delivered at the blood clot and create better penetration; as such, the plasminogen can be bound to a new site to enhance the effect of chemical thrombolysis; significant enhancement was both achieved in in vitro [64] and in vivo [65] ischemic stroke mouse model studies. Similarly, nanomaterial functionalized methods have also been used to improve the targeting of tPA therapy. A recent study, conducted by Chauvierre et al., demonstrated that tPA-fucoidan-coated nanomaterials were able to bind the P-selectin of activated platelets in thrombus due to the nanomolar affinity between fucoidan and P-selectin. As a result, the therapeutic dose and hemorrhagic complications of tPA were dramatically reduced, and the time window of tPA treatment could be much wider. However, the cytotoxicity and systemic side effects of these nanomaterials are still a big challenge [66].

Reperfusion injury is caused by the free radicals like reactive oxygen species (ROS), reactive nitrogen species (RNS), and nitric oxide (NO) from injured cells, inflammatory cells, and endothelial cells that are stimulated when blood is restored in ischemic brain tissue [67, 68]. However, the direct use of free radical scavengers has not been reported to be able to achieve pleasant clinical results. To overcome these limitations, scientists shifted the gear to synthesize all kinds of

TABLE 1: List of the application of nanomaterials for the neurodegenerative diseases.

Type	Nanomaterials	Drugs delivered	Disease	Findings	Disadvantages	References
Lipid-based nanomaterials	Prp CsiRNA-RVG-9r-liposomes	Prp CsiRNA RVG-9rPrp Cs	Neurodegenerative protein misfolding diseases (NPMD)	Increase delivery efficiency, prolong half-life of drug in peripheral circulation, and increase BBB passage rate.	In animal experiments, mice treated with nanomaterials have a certain probability of causing type III acute allergic reaction.	[18]
	Fus-liposomes-rhFGF20	rhFGF20	Parkinson's disease (PD)	Extend drug half-life, high encapsulation rate, increase BBB penetration ability, slow-release drugs, targeting, high biocompatibility.	Not mentioned.	[19]
	RVG29-liposomes	N-3,4-Bis(pivaloyloxy)-dopamine	PD	High BBB penetrability, high biocompatibility, striatum nigra targeting, drug sustained release.	Not mentioned.	[20]
	PEG-liposomes-MBs	GDNF+Nurr1	PD	Ultrasound-guided ability, ultrasound-guided BBB penetration ability, sustained release, and extended drug half-life.	Poor BBB penetration.	[21]
	RMP7-lf-PEG-liposomes	Quercetin	Alzheimer's disease (AD)	High BBB penetration ability, SK-N-MC cell targeting, drug sustained release.	May be able to induce inflammation.	[22]
	NGF-SM-ApoE-liposomes	Nerve growth factor, surface serotonin modulator, ApoE	AD	Maintain NGF activity, high biocompatibility, high BBB permeability, A β 1-42 and SK-N-MC cell targeting, sustained release of contents.	Not mentioned.	[23]
	Nanomicellar system (SANS)	L-DOPA	PD	Autonomous formation, easy to manufacture, epidermal permeability, drug sustained release.	Lack of targeting.	[24]
	LD crystalsomes (micellar)	L-DOPA	PD	Autonomous formation, easy to manufacture, drug sustained release, good biocompatibility, higher drug delivery efficiency.	The biological toxicity is not clear.	[25]
	Pluronic P85/F68 micelles	Baicalin	PD	Self-forming, stable character suitable for oral administration, sustained release, enhance content of crossing BBB capacity, enhance content of cell accumulation.	Weak BBB permeability, may cause damage to the structure and function of mitochondria.	[26]
	Mixed-shell polymeric micelle (MSPM)	None	AD	A β deposits are targeted, A β deposits have strong affinity, reduce the production of proinflammatory factors, have good BBB permeability and strong biocompatibility.	Longer metabolic time.	[27]
Polymeric nanomaterials	C(NCAM-C3)T(TPP)-N(nano)M(micelle)	Resveratrol	AD	Automated assembly, good BBB permeability, high encapsulation efficiency, mitochondrial targeting, cumulative, drug sustained release, reduce expression of proinflammatory factors.	Longer metabolic time.	[28]
	Micelle	Curcumin	AD	Automatic formation, good drug encapsulation rate, drug sustained release, BBB permeability.	Not targeted itself.	[29]
	PAMAM dendrimers	Carbamazepine	Neurodegeneration (ND)	Improve the solubility of the package, increase the stability of the package, good drug packaging ability,		[30]

TABLE 1: Continued.

Type	Nanomaterials	Drugs delivered	Disease	Findings	Disadvantages	References
				reduce the package of peripheral and cellular toxicity, good biocompatibility.	Not resistant to acid and alkali, high concentration, easy to kill, drug sustained release ability is poor.	
	G4HisMal-dendrimers	Boc-L-histidine	AD	High BBB permeability, good biocompatibility, $A\beta$ (1–40) targeting.	Not mentioned.	[31]
	Lactoferrin coupled PAMAM dendrimers (PAMAM-If)	Memantine	AD	Drug sustained release, controlled release, extended drug half-life, good encapsulation ability, high drug delivery efficiency, good BBB penetration, and brain targeting.	Have some blood toxicity.	[32]
	Phosphorus dendrimers	Phosphorus	PD	Some anti-HIV ability, inhibition of -SYN fibrosis.	Hematotoxicity.	[33]
	Carbosilane dendrimers	None	PD	Inhibits ASN fibrillation, reduces ROS, and protects nerve cells.	Not mentioned.	[34]
	Dopamine-loaded PLGA nanomaterials	Dopamine	PD	Prolonged half-life, slow-release, controlled-release, decreased peripheral circulation toxicity, good biocompatibility, decreased Ros, striatum targeting, BBB permeability.	Cause inflammation in the targeted area.	[35]
	Collagen-coated PLGA	None	PD	Good cell adhesion, good biocompatibility, and certain ability to promote cell growth.	Not mentioned.	[36]
	PLK2-PLGA-NP	PLK2	PD	Inhibition of drug degradation, improvement of enzyme stability and long-term drug release, good biocompatibility and strong encapsulation ability.	Not mentioned.	[37]
	Fe_3O_4 -PEG/PLGA-OX26	Magnetic Fe_3O_4 nanoparticles, OX26	AD	Strong drug loading, magnetic targeting, biocompatibility, sustained release, controlled release.	Larger particles.	[38]
	Hollow gold nanoparticles	Xanthoceraside	ND	Large drug loading, increased drug solubility, can be traced.	No targeted ability	[39]
	Hollow au/Ag nanostars	None	ND	Large surface area, high Raman spectrum activity, and high near-infrared light sensitivity.	Unknown biological toxicity.	[40]
	Concave cubic Qu-P80-AuPd	Quercetin	AD	Good biocompatibility, good BBB penetration, high loading capacity, low cytotoxicity, good biocompatibility, lysosomal targeting.	Not mentioned.	[41]
Inorganic nanomaterials	GNRs-APH-scFv, GAS	Thermophilic acylpeptide hydrolase	AD	Good biocompatibility, strong photothermal effect, near infrared light sensitivity, low toxicity, stable physical and chemical properties.	Self-BBB penetration is slightly worse.	[42]
	Single-wall carbon nanotubes and gold nanoparticles modified screen-printed electrodes	None	PD (dopamine monitoring)	High sensitivity, good stability, small damage, real-time monitoring.	Not mentioned.	[43]
		None	PD (early diagnosis)	High sensitivity, high detection accuracy, high degree of integration of DOPA.	Not mentioned.	[44]

TABLE 1: Continued.

Type	Nanomaterials	Drugs delivered	Disease	Findings	Disadvantages	References
	Functionalized random networks of carbon nanotube RN-CNT					
	Carbon nanotubes (CNTs)	None	PD	Reduce glial cell proliferation, increase stem cell proliferation, good biocompatibility.	Not mentioned.	[45]
	SWCNT-PEGs-If	L - 1 6-hydroxydopamine	PD	Striatal targeting, high biocompatibility, good BBB permeability, strong drug loading capacity, low toxicity, sustained release.	Cause a certain inflammatory response.	[46]
	EMT nanomaterials	None	AD	Inhibition of fibrinogen interactions in abnormal clots.	Not mentioned.	[47]
	SBA-15 (silica holed nanorod)	L-DOPA	PD	Has good BBB permeability, good drug loading, and good biocompatibility.	No targeted ability.	[48]

novel nanomaterials with free radical scavengers like tocopherol [69], ascorbic acid [70], and melanin [71]. As a study reported by Liu's group, they conjugated melanin with nanomaterials to form a novel material, which could not only effectively scavenge the free radicals in a rat stroke model but also sufficiently inhibit the expression of inflammatory mediators. What is more important is that this biomaterial obtained fairly good biocompatibility, resulting in very minor adverse reactions to the degree that the human body could totally ignore [71]. In addition, antioxidant enzymes have also received widespread attention since they are more effective at removing free radicals than free radical scavengers. For instance, Yun and his colleagues combined superoxide dismutase (SOD) enzyme with multiple nanomaterials (liposomes, polybutylcyanoacrylate (PBCA), or poly lactide-co-glycolide (PLGA)) and added targeting antibodies. In vivo experiments show that this modified nanomaterial significantly reduced the infarct area in the hippocampus region after stroke by more than 50% [72]. Interestingly, nanoscale exosomes secreted by a variety of cells have been shown to improve the prognosis of stroke significantly [73–76]. Due to the complexity of exosome components, the underlying mechanism regarding the neuroprotective effect is really hard to explain. However, exosomes' certain properties, such as no cytotoxicity and ability to carry a variety of lipids, proteins, and nucleic acids through the BBB, may contribute to the therapeutic effect after stroke [77]. Put together, by leveraging the novel nanotechnology and nanomaterials in the neuroprotective medicine, the faster delivery, more biocompatible and efficient neuroprotective drugs that could be synthesized, and the better therapeutic strategies and approaches could be provided to eventually overcome the challenges we are facing right now.

2.3. Nanomaterials for Drug Delivery across the Blood-Brain Barrier. BBB is a multicell-composed membrane between the peripheral blood and the brain [78]. It not only blocks most pathogens from invading the brain but also prevents the entry of most drugs for targeting neurological diseases [79], except for those small lipophilic molecules with a molecular weight less than 400–500 Da and confined amount of hydrogen bonds less than 9–10, which can pass through the BBB [80]. In addition, even if the drug enters the brain smoothly, a large proportion of the active ingredients will be degraded or eliminated from the brain [81]. Such unique anatomical structure and physiological characteristics determine that lots of medicines that act in the brain seem very challenging. Therefore, many researchers around the world are trying to find novel solutions to address these situations by providing a better drug delivery system to penetrate the BBB, while maintaining sufficient drug activities.

Based on current researches, four major strategies were widely considered: (i) Bypassing the BBB, including methods like intracerebroventricular, intracerebral, intrathecal, intratympanic, and intranasal [82]. However, the limitations of invasiveness, cytotoxicity, and low efficiency make it an unsuitable method. (ii) BBB manipulation, focusing on increasing the permeability of the blood-brain barrier, but the consequence is that peripheral pathogens can also enter

the brain, causing diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and intracranial infection [83, 84]. (iii) Drug modification, including improving drug liposolubility and modifying the drugs to increase the binding affinity with the specific receptors or carriers on BBB [85]. (iv) Nanomaterial-based drug delivery system (Figure 1), nanomaterials with multiple modifications could penetrate the BBB and localize to the brain tissues quickly and accurately, reducing enzymatic degradation, improving drug stability, and therefore maintaining a stable drug concentration to achieve the best therapeutic effect [86, 87]. Undoubtedly, due to the fact that the method involves easy modification of nanomaterials, this drug delivery system will be the focus of future scientists' research.

At present, various nanomaterials are used in biopharmaceutical research, including lipid-based nanomaterials, polymeric nanomaterials, and inorganic nanomaterials. One of the most promising biomaterials is the lipid-based nanomaterials, because of their stability and nontoxicity. Among which, the most well-reported lipid-based nanomaterials are liposomes as discussed below.

Liposomes are composed of phospholipid bilayers surrounding a hydrophilic core [88]. This structure gives liposomes the ability to support both hydrophilic and hydrophobic molecules, and these nanomaterials can be easily modified to make them stable and effectively localized in the specific cells after passing through BBB [89]. For example, a novel Y-shaped multifunctional targeting material c(RGDyK)-pHA-PEG-DSPE was designed to be incorporated with liposomes (c(RGDyK)-pHA-LS). In which, c(RGDyK) and pHA could circumvent the blood-brain tumor barrier (BBTB) and BBB, respectively. And the PEG-DSPE was added to escape the liposomal removal function of the reticuloendothelial system (RES). A multiple-ligand structure gives it an ability to circulate stably in the blood and target brain tumor cells specifically. In vitro and in vivo studies demonstrated that doxorubicin- (DOX-) loaded c(RGDyK)-pHA-LS display a better therapeutic effect than the DOX-loaded liposome only group [90]. This result indicated that more functional ligands should be applied to nanomaterial synthesis. For instance, monoclonal antibodies and receptor substrates were used as liposome ligands to allow more precise binding of nanomaterials to the BBB [91–93]. However, these receptors are distributed throughout the body, reducing the specificity of these nanomaterials. Corresponding side effects are also caused by the activation of receptors at various positions. Lipid-based nanomaterials also include solid lipid nanomaterials (SLN), which possess benefits like biocompatibility, improved drug stability, and massive load capacity and provided a controlled drug release within a few weeks. Although these nanomaterials have low hydrophilic molecular loading capacity and some special preparations in application, they are considered to have great potential in drug delivery [94, 95].

The other two nanomaterials, including polymeric nanomaterials and inorganic nanomaterials, are also hotspots of research. But same as lipid-based nanomaterials, there are still many restrictions waiting to be overcome. Ideally, safe

FIGURE 1: CNS drug delivery system. Nanomaterials composed of nanoscale carrier, drugs, and multiple functionalized ligands can penetrate the BBB and localize to the cancer cells through receptor-mediated endocytosis. This strategy allows the drug to exert a powerful killing effect on cancer cells and effectively reduces the off-target effect on healthy cells. CNS: central nervous system; BBB: blood-brain barrier.

nanomaterials that could be loaded with various drugs and be able to target the specific cells in the brain remotely are highly expected.

2.4. Nanomaterial Stem Cell Hybrids for Neuroscience. Stem cell transplant therapy using neural stem cells (NSCs), embryonic stem cells, mesenchymal stem cells (ESCs), or induced pluripotent stem cells (iPSCs) has been considered as a potential therapeutic strategy for neurological diseases, including stroke, brain trauma, PD, AD, and brain tumor [96]. The low survival rate of transplanted stem cells is the major reason why the majority of clinical trials fail. 30% of embryonic stem cells died within 3 days after transplantation into a rat stroke model, caused by reasons like immune rejection, lack of trophic factors, and extracellular matrix [97, 98]. Although there are a lot of studies reporting that the preconditioning of stem cells [99] or lesion microenvironment [100] may help to increase the cell survival ratio and acquire better prognosis, the limitations and challenges still remain [101, 102]. Recently, nanomaterial-composed scaffolds were used to facilitate stem cell transplantation therapy [103, 104]. Carbon nanotubes (CNTs) are considered promising nanomaterials due to their excellent electrical conductivity, which is beneficial for stem cell differentiation and intercellular communication [105]. Kam and his colleagues have synthesized laminin-SWNT (single-walled carbon nanotube) thin films in order to mimic the structure of living tissues in the human body, in which laminin is a significant part of the extracellular matrix. An *in vitro* study demonstrated that this material could support proliferation and differentiation of NSCs, indicated by the presence of synaptic connections [106]. Similarly, scaffolds like collagen/MMA/acrylic acid (PMMAAA) [107], poly-L-lactic acid-co-poly-(3-caprolactone)/collagen

[108], terpolymer/collagen [109], poly-L-lactic acid (PLLA) [110], and poly(lactic-co-glycolic acid)/praphene oxide-l-theanine (PLGA/GO-TH) [111] are synthesized to enhance stem cell survival and promote the differentiation.

Interestingly, some nanomaterials even could be absorbed by stem cells and quickly spread throughout the cells. A nanomaterial with superparamagnetic iron oxide (SPIO) as the core and ZnO as the shell could be absorbed by human adipose tissue-derived stem cells (hATSC), and then, the transcription factors could be activated to modulate the neurogenesis [112]. In another study, retinoic acid- (RA-) loaded nanomaterials were taken up by NSC and the RA could be further released in the cells, leading to the activation of the SAPK/JNK signaling pathway and ultimately influencing the proneurogenic genes to benefit the differentiation of neural stem cells *in vitro* and *in vivo* [113]. This study suggested that some cell growth regulators could possibly be loaded to the nanomaterials as well and eventually acquire better effects. For instance, fibroblast growth factor receptor-1 (FGFR1) and its FGF-2 ligand were delivered into the brain subventricular zone, and the release of these growth factors could stimulate the neurogenesis in the adult brain [114].

Of course, transplantation therapy also faces the problem of a lack of monitoring system. Scientists in many fields are trying to build a nanomaterial-based imaging agent, which requires merits like long half-life, high selectivity, contrast-to-noise enhancement, and noncytotoxic. An amphiphilic fluorophore-derived nanomaterial with aggregate-induced emission (AIE) effect and self-assembly ability was used to label human embryonic stem cells (hESC) and monitor their differentiation. Experiments show that this monitoring could last for 40 days and has better fluorescence intensity and

biocompatibility [115]. These nanomaterials could also be radioactive, magnetic, paramagnetic, superparamagnetic, and electron-dense [116–121], which can be monitored by commercially available equipment (magnetic resonance imaging (MRI), computed tomography (CT), or fluorescence tomography (FT)) easily. However, the toxicity of nanomaterials to stem cells remains an open question.

3. Therapeutic Nanomaterials for Cancer

3.1. Nanomaterials as Immune-Modulating Agents. The biological immunity of cancer cells is divided into three steps: (i) cancer cells recognized by the immune system, (ii) targeting of the cancer cells for specific elimination, and (iii) immune system destroying cancer cells effectively [122]. Significant progress has been made in the field of cancer immunotherapy by regulating the human immune system to eliminate cancer cells. However, the problems of immune changes and delivery efficiency at nontumor sites caused by the systemic delivery of immunomodulatory compounds have not been well addressed, resulting in the limited application of immunotherapy. Nanotechnology offers a lot of innate advantages in these aspects. Combining immunomodulatory compounds by covalence conjugation [123], chelation [124], encapsulation [125], etc., can increase the functional efficacy of the immunomodulatory compounds and reduce their depletion in the peripheral circulation to avoid unnecessary immune responses.

Lipid-based nanomaterials and polymeric nanomaterials have good encapsulation capabilities. The modification of such nanomaterials makes it easier to obtain a single stable targeting than other materials or immunomodulatory compound only approach, therefore making it more reliable and controllable [126]. For inorganic nanomaterials, under certain conditions, they can become immunomodulators themselves. This is undoubtedly a huge distinctive advantage compared to other immune presenters that require targeted controlled release. For example, gold nanomaterials could produce a photothermal effect after receiving near-infrared light to stimulate the immune system to work, and gold nanomaterials are easily engulfed by monocytes [127].

At present, the application of nanomaterials in immunomodulatory therapy is mainly focused on the targeted delivery of immunomodulators and enhanced immune recognition of tumor cells [128, 129]. It is worth mentioning that a special nanomaterial used in immunomodulatory therapy is the virus-like particle (VLP). VLPs can be efficiently absorbed, processed, and presented by MHC class II molecules of DCs, thereby activating T cells. In addition, unlike many soluble antigens, VLPs efficiently cross-present through APCs via the class I MHC pathway, thereby activating CD8⁺ T cells [125].

3.2. Nanomaterials as Anticancer Drug Delivery System. Cancer is now responsible for the majority of global deaths and is expected to be the single most important obstacle to increase life expectancy in the 21st century [130]. Nanocarrier-targeted drug delivery systems have the potential to circumvent several shortcomings of conventional therapeutic for-

mulations. Nanomaterials with special ligand functionality can efficiently target cancer cells [131]. Moreover, nanomaterials can be designed for improving the solubility and stability of anticancer drugs, increased drug loading, improved half-life in the body, controlled release, and selective distribution by modifying their composition, size, morphology, and surface chemistry [132].

As an anticancer drug delivery system, it can be divided into three parts. The first part is the carrier, which refers to a variety of nanomaterials, such as metal nanomaterials, carbon-based materials, liposomes, and dendritic and macromolecule polymer nanomaterials [133]. Metal and metal oxide nanomaterials are ideal anticancer drug carriers due to their controllable size and shape, easily modified surface functionalization, and good biocompatibility. A recent study showed that docetaxel coupled with gold-doped apatite has anticancer effects in vitro. The material showed higher cytotoxicity to human liver cancer cell line HepG2 and showed improved bioavailability [134]. Carbon-based nanomaterials have many advantages, such as large specific surface area, high drug loading, and easy surface modification. They have also been widely studied in imaging, drug delivery, and diagnosis of tumors [135]. Recently, the study of drug delivery by multiwalled carbon nanotubes (MWCNTs) has shown that the release of drugs in the tumor site and the absorption of cells have shown the potential for the treatment of multidrug-resistant tumors [136]. Liposomes are the first nanomaterials to be used; it can prolong the circulation time of the drugs and reduce toxicity to healthy tissues around. Correspondingly, these vehicles offer several other advantages including biocompatibility, self-assembly, and high drug cargo loading [137]. Another polymer nanomaterial platform that has received much attention as a drug delivery system is polymer micelle nanomaterial. Recently, Peng et al. prepared a polymer micelle by combining temozolomide (TMZ) and anti-bcl-2 siRNA with a folic acid triblock copolymer to overcome the limitations of acquired drug resistance of glioma cells and BBB on drug delivery [138].

The second part is the combination and release of drugs with nanomaterials, such as the encapsulation of drugs by liposomes, or the modification of metals and metal oxide nanomaterials by drugs, and then the release of drugs through REDOX, pH-mediated release systems, or other stimulation methods, such as magnetic field, ultrasonic induction, and electrochemical triggering.

The third part is the targeted drug delivery system. Targeting can be divided into active and passive targeting. Passive targeting refers to the accumulation of nanomaterials in tumor sites due to the vascular barrier destruction and poor lymph node clearance in tumor sites. Active targeting is ligand-mediated targeting, including recognition and uptake of substrate [139, 140]. The system includes ligands like antibodies, proteins, nucleic acids, peptides, vitamins, and other organic molecules. Substrates can be molecules on the surface of cancer cells, substances in the internal environment of cancer cells, or proteins secreted by cancer cells [141, 142]. For example, Au nanomaterials coated with nuclear localizing signal (NLS) were able to escape the endosome and penetrate the nucleus of cancer cells to induce

TABLE 2: List of nanomaterials in cancer therapy.

Type	Nanomaterials	Drugs delivered	Disease	Findings	Disadvantages	References
Lipid-based nanomaterials	Liposomal annamycin	Annamycin	Acute lymphocytic leukemia, acute myeloid leukemia	Bypass multidrug resistance mechanisms of cellular drug resistance	Diarrhea, typhilitis, and nausea	[148]
	Liposomal doxorubicin	Doxorubicin	Non-Hodgkin's lymphoma	Prolong systemic circulation, a ligand for cell-specific targeting, and an imaging agent for diagnosis	Induce infusion reactions about activating the complement cascade	[149]
	Liposomal vincristine	Vincristine	Non-Hodgkin's lymphoma	Reduce neurotoxicity and increase dose intensity delivery	The risk of peripheral neuropathy	[150]
	Liposomal cisplatin	Cisplatin	Progressive osteogenic sarcoma metastatic to the lung	High reactivity, affinity to biomolecules, and low release rate at the tumor site	Possible immune-related reactions or the blood clearance in the case of PEGylated liposomes	[151]
	Docetaxel-loaded solid lipid nanomaterials	Docetaxel	Breast cancer Lung metastasis	High stability for at least 120 days	Short lifespan, poor durability, poor encapsulation	[152]
	Cisplatin-loaded solid lipid nanomaterials	Cisplatin	Breast cancer	Overcome dose-related toxicity, enhance targeting	Require additional microwave-assisted equipment	[153]
	HPMA copolymer—DACH platinate	ProLindac	Ovarian cancer	Increase platinum accumulation in tumors via the enhanced permeability and retention effect	Nausea and vomiting	[154]
	Polymer-lipid hybrid nanomaterials	Doxorubicin	Solid tumors	Prolong drug release, enhance systemic half-life, decrease toxicity, and targeted drug delivery	Potential biotoxicity of nanomaterials	[155]
	Poly(ethylene glycol)-block-poly(L-lactic-co-glycolic acid)	Docetaxel	Prostate cancers	Have good biocompatibility and effective cancer cell inhibition ability	Have potential biotoxicity due to slow drug clearance	[156]
	Folic acid-PAMAM dendrimers	Methotrexate	Epithelial cancer	Increase its antitumor activity and markedly decreased its toxicity	The optimal dose of targeted drug has not been definitively established	[157]
Polymeric nanomaterials	Poly(glycerol-succinic acid) dendrimers	Camptothecin	Various cancers	Enhance anticancer activity	Limit water solubility and resulting suboptimal pharmacokinetics	[158]
	Superparamagnetic iron oxide nanomaterials	Doxorubicin	Liver cancer	Enhance the biological effects of doxorubicin	Certain hepatorenal toxicity	[159]
	AOT-alginate nanomaterials	Doxorubicin	Breast cancer	Enhancement of therapeutic effect	Some cardiotoxicity	[160]
	Glycol chitosan nanomaterials	Doxorubicin	Solid tumors	Exhibit excellent tumor-homing efficacy, an effective strategy to overcome multidrug resistance	Low solubility	[161]
	Anti-HER2 antibody-targeted gold nanomaterials	Nanoshell-assisted infrared photothermal therapy	Metastatic breast cancer	Retain high antimitotic potency, which could contribute to a higher therapeutic index in high EPR tumors	Potential biotoxicity	[162]
	Inorganic nanomaterials		Breast cancer	Reduce hepatic and renal toxicity	Some hepatic and renal toxicity	[163]

TABLE 2: Continued.

Type	Nanomaterials	Drugs delivered	Disease	Findings	Disadvantages	References
Special category	Silica-based nanomaterials	Organotin metaldrug				
	Aminosilane-coated iron oxide nanomaterials	Thermotherapy	Brain tumors	Low toxicity, the possibility of radical cure	Complex operation, need further exploration	[164]
	Nanocrystalline 2-methoxyestradiol	Panzem NCD	Various cancers	Delivery of poorly water-soluble drug	Fatigue, nausea, mild transaminitis, and dysgeusia	[165, 166]
	NID-biopolymer nanocomposites	Doxorubicin	Liver cancer	Prolong and continue release of antitumor drugs	Complicated technology	[167]
	Paclitaxel nanomaterials in porous	Paclitaxel	Solid tumors	Favorable preclinical safety and antitumor activity profiles	Fatigue, alopecia, nausea, vomiting, neuropathy, anorexia, and myalgia	[168]
	Albumin-bound nanomaterials	Doxorubicin, methotrexate	Various cancers	Decrease the glycolysis and metabolic tumor volume	Decrease antibody presence in the general circulation, which might lead to undesirable effects	[169]

DNA damage [143]. And nanomaterials coated with polyethylene glycol (PEG) achieve passive targeting of tumor tissue through EPR effect. The invisible coating of PEG and other polymers prevents the adsorption of serum proteins, increases cycle time, and increases the probability of particle penetration of tumor tissue [144]. When multiple ligands are combined with nanomaterials, their targeting also can be improved [145].

At present, multiple nanomaterials (Table 2) were demonstrated to benefit from cancer treatment, but due to their particularity, the biological toxicity of nanomaterials is still the major focus that we cannot ignore [146, 147].

3.3. Nanomaterials as a Combination Therapy for Cancers. Traditional single-drug or multidrug combination chemotherapy tends to produce serious adverse consequences due to the accumulation of drugs and their metabolism in vital organs. Moreover, tumor cells are prone to multidrug resistance, and the efficacy of chemotherapy drugs is often not up to the expected effect [170, 171]. In medical applications, liposomes and polymeric nanomaterial conjugates are the two major categories, accounting for more than 80% of all nanomaterial drugs.

Liposome is a kind of spherical lipid vesicles with a double-membrane structure. It is widely used as a drug carrier by reasons that it can effectively encapsulate hydrophilic and hydrophobic drugs to avoid adverse external stimuli and carry specific ligands to identify specific cell tissues and organs. For example, Doxil was the first liposome drug approved by the FDA for the treatment of Kaposi's sarcoma. It wraps doxorubicin (a widely used anticancer chemotherapy drug) in a liposome carrier to significantly extend the half-life of doxorubicin and increase the accumulation of the drug in tumor tissue [172, 173].

Another research hotspot is polymer-drug coupling of polymeric nanomaterials. The combination of small molecule drugs with polymeric nanomaterials can improve adverse reactions. It also enhances the passive delivery of drugs to leaky tumor tissue [174, 175]. In addition, metal nanomaterials and ceramic nanomaterials have demonstrated some specific therapeutic potential such as amino-silane-coated iron oxide nanomaterials, which have recently been used in brain tumors treated with thermotherapy; the survival time was prolonged by 4.5 times by means of magnetic field-induced excitation of iron oxide superparamagnetic nanomaterials and hyperthermia in a rat model [176].

In addition to the anticancer drugs that can inhibit or kill tumor cells, the interaction between nanomaterials and intracellular organelles also plays an important role in cancer treatment [177]. For example, lysosomes and endolysosomes of endogenous foreign bodies are used to monitor cell apoptosis cascade, calcium cycle, and ATP synthesis. The nucleus consists of DNA mutation, gene expression, cell proliferation, endoplasmic reticulum [178], and other Golgi complexes, which promote protein synthesis and transport to other organisms [179]. Despite recent breakthroughs in the research of nanomaterials in the field of tumors, more in-depth exploration is needed, such as the optimal properties of various nanomaterials, the numerous biological

barriers faced by nanomaterials, and the related cytotoxicity of nanomaterials.

4. Conclusion and Future Directions

As discussed above, nanomaterials have proved their importance in the medical field and provided new directions for the treatment of neurological diseases and cancers, although the disadvantages are remaining, such as lack of specialized equipment for efficient and high-quality nanomaterial synthesis, difficulty of assessing its safety and effectiveness, and some shortcomings of specific materials mentioned above. Future directions of nanomaterials should be in line with the following principles: (1) diameter within 100 nm, possess high scalability, and easy to be degraded; (2) low cost and high productivity; (3) biocompatibility, nontoxic, and without initiating the pathological processes like inflammation and thrombosis; (4) highly sufficient targeting and ability to penetrate multiple biological barriers, like BBB; (5) stable in the blood and resistant to be cleared by RES; and (6) loaded molecules could be released smoothly and achieve significant therapeutic effect for the diseases. In conclusion, the treatment of neurological diseases or cancers, in this regard, is an uphill battle that might be easily overcome with nanotechnology if solutions such as multimodal agents are actively practiced. Nevertheless, the future still holds promises for the field of nanomedicine to be exploited to its fullest extent for the potential advanced therapeutic approaches.

Abbreviations

AD:	Alzheimer's disease
AIE:	Aggregate-induced emission
ALS:	Amyotrophic lateral sclerosis
BBB:	Blood-brain barrier
BBTB:	Blood-brain tumor barrier
CNS:	Central nervous system
CNTs:	Carbon nanotubes
CT:	Computed tomography
DOX:	Doxorubicin
ESCs:	Mesenchymal stem cells
FGFR1:	Fibroblast growth factor receptor-1
FT:	Fluorescence tomography
hATSC:	Human adipose tissue-derived stem cells
iPSCs:	Induced pluripotent stem cells
MRI:	Magnetic resonance imaging
MS:	Multiple sclerosis
MWCNTs:	Multiwalled carbon nanotubes
NLS:	Nuclear localizing signal
NO:	Nitric oxide
NSCs:	Neural stem cells
PBCA:	Polybutylcyanoacrylate
PD:	Parkinson's disease
PEG:	Polyethylene glycol
PLGA:	Poly lactide-co-glycolide
PLLA:	Poly-L-lactic acid
PMMAA:	Collagen/MMA/acrylic
RA:	Retinoic acid
RES:	Reticuloendothelial system

RNS:	Reactive nitrogen species
ROS:	Reactive oxygen species
SLN:	Solid lipid nanoparticle
SOD:	Superoxide dismutase
SPIO:	Superparamagnetic iron oxide
SWNT:	Single-walled carbon nanotubes
tPA:	Tissue plasminogen activator
TMZ:	Temozolomide
VLP:	Virus-like particle.

Conflicts of Interest

The author(s) declare(s) that they have no conflicts of interest.

Authors' Contributions

KW, XZ, and EY wrote the first draft. PD, HW, CZ, JY, and JH revised and edited the final manuscript. QZ, JY, and JH supervised the manuscript and provided critical input. All authors gave feedback and agreed on the final version of the manuscript.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 81771262), Zhejiang Health Science and Technology Project (2016RCA022), Zhejiang Key Research and Development Project (2017C03027), and American Heart Association Predoctoral Fellowship for JH (19PRE34380114).

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