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Review Article

Recent Advances in FePt Nanoparticles for Biomedicine

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FePt nanoparticles have great potential for biomedical applications due to their superior characteristics, including superparamagnetism, resistance to oxidation, and high chemical stability. The present paper reviews the methods used to prepare FePt nanoparticles, surface modifications, and their applications in the biomedical field, such as biosensing, magnetic resonance imaging (MRI), targeted drug delivery, and therapy.

1. Introduction

In the past several decades, the biomedical applications of magnetic nanoparticles (MNPs), including their use as MRI contrast agents and carriers for targeted drug delivery and in magnetic fluid hyperthermia (MFH), biological separation, and immunodetection, have become the topic of considerable research, and significant progress has been made in these fields [1–5]. MNPs mainly include metallic oxide nanoparticles (e.g., Fe_3O_4 and γ-Fe_2O_3), metallic nanoparticles (e.g., Fe and Co), and metal alloys (e.g., FePt and FeCo). Among them, iron oxide nanoparticles (IONP) are the most frequently investigated due to their advantages of superparamagnetism, good biocompatibility, being biodegradable, and easy synthesis. They have been used for the purposes of diagnosis and therapy [6–12]. Branca et al. [7] reported that the cancer-binding ligands functionalized IONP combined with hyperpolarized ^{3}He MRI could detect early-stage metastatic lung tumors in mice. Andreas et al. [8] demonstrated the citrate-coated superparamagnetic iron oxide nanoparticles (SPIONs) as MRI contrast agents could be employed in human mesenchymal stem cell labeling and tracking. Mahmoudi et al. [9] reported that drug-loaded SPIONs could potentially be guided to the desired target site under an external magnetic field. However, metal alloy nanoparticles, such as FePt nanoparticles, with better magnetic properties, have also attracted increasing attention from many researchers. The FePt nanoparticles can show excellent superparamagnetic property and be chemically stable against oxidation [13]. In addition, the FePt nanoparticles can be prepared with tunable size and shape and could be modified for diverse biomedical applications [14]. The present paper reviews advances in FePt nanoparticle preparation, surface modification, and biomedical applications in recent years and their future prospects.

2. Preparation and Properties of FePt MNPs

FePt nanoparticles mainly include two structures. One structure consists of a disordered face centered cubic (FCC) structure (cf. Figure 1(a)). The other structure consists of an ordered face centered tetragonal (FCT) or ordered $L1_0$ phase (cf. Figure 1(b)). Due to their good magnetocrystalline anisotropy, high coercivity, high magnetic energy product, specific Curie temperature, and low superparamagnetic critical size, FePt nanoparticles are suitable for applications such as ultrahigh density magnetic recording media and vertical magnetic tunnel junctions [15–20]. In addition, superparamagnetic FePt nanoparticles, which have good biocompatibility and high X-ray absorption, have potential applications in biomedicine [21, 22].

Various methods are available for the preparation of FePt MNPs, including mechanical cold deformation [23],

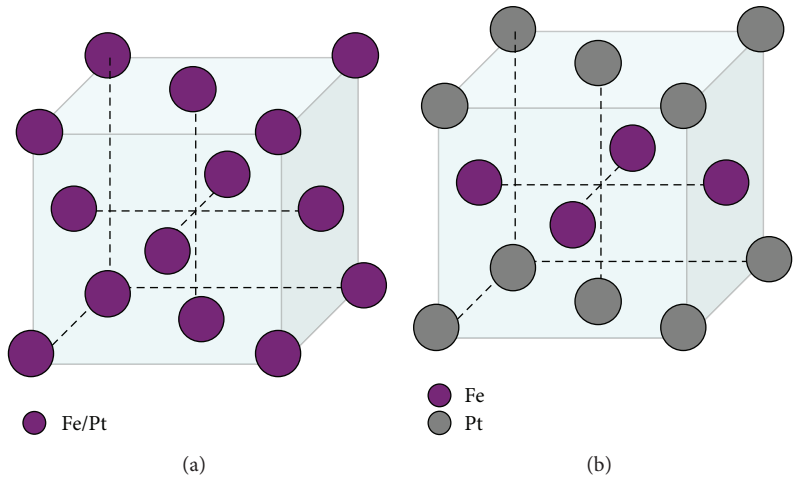

Figure 1: FePt crystal structure: (a) FCC structure; (b) FCT structure.

magnetron sputtering [18, 24, 25], vacuum deposition [26], and some chemical techniques.

2.1. Physical Methods

2.1.1. Mechanical Cold Deformation Method. The general mechanical cold deformation procedure consists of cold drawing, rolling, and extrusion. Using this method, Hai et al. [23] obtained ordered FePt material with high anisotropy by heating Fe and Pt metals, which were circularly rolled, in a sealed vacuum quartz tube. This strategy can be used for large-scale production due to its relatively simple technique. However, it is not easy to control the mutual diffusion of Pt and Fe, and the properties of the product are also difficult to control.

2.1.2. Magnetron Sputtering Method. In a vacuum with an appropriate amount of inert gas (typically Ar) and a certain voltage, Ar+ can impact the Fe target, Pt target, or other alloy targets to cause the Fe and Pt atoms on the surface of the targets to be sputtered out. Under the influence of the magnetic and electric fields, the sputtered Fe and Pt atoms may be transferred to the substrate and deposit to form a FePt nanomaterial. This process is called magnetron sputtering and is one of most widely used methods. FePt films have been successfully prepared by this method [18, 24, 25]. Weller et al. [24] used high-temperature sputtering to prepare highly chemically ordered $L1_0$ FePt films in a glass dish coated with adhesion, heat sinks, and a deformation layer by adding Ag to reduce the required deposition temperature and Cu to reduce the Curie temperature.

2.1.3. Vacuum Evaporation Deposition Method. The vacuum evaporation deposition method is described as follows. First, the reaction chamber is placed in a strong vacuum. After heating, the objective material can evaporate and deposit on the smooth substrate. Then, the desired nanomaterials are obtained. Yu et al. [26] reported the production of FePt films grown on a MgO (110) single-crystal substrate (where the temperature was heated to 700°C) by electron-beam coevaporation. Castaldi et al. [27] prepared FePt nanoparticles, which were thermally deposited on oxidized Si substrates (substrate temperatures of 300–700°C) by electron-beam coevaporation of Fe and Pt.

2.2. Chemical Methods.

However, when using these physical methods, it is not easy to specify the morphology, particle size, and size distribution of FePt MNPs. To overcome these shortcomings, several chemical methods have been developed in the past decades in which the stoichiometry, size, and shape of FePt MNPs can be controlled. The general chemical strategies used to obtain FePt MNPs include high-temperature thermal decomposition reduction, polyol reduction, microemulsion methods, and electrochemical deposition methods.

2.2.1. Thermal Decomposition Reduction. Thermal decomposition deacidizing is another method used to prepare MNPs through heating and reducing the organic metal compound (precursor) in a high-boiling-point solvent with a surfactant. This method can yield particles with a tunable size and high crystallinity. In 2000, using oleic acid and oleylamine as surfactant, Sun et al. [28] prepared monodispersed FePt nanoparticles with a 4 nm diameter by thermally decomposing iron pentacarbonyl ($Fe(CO)_5$) and deacidizing platinum acetylacetonate ($Pt(acac)_2$) in a solvent of octyl ether. Subsequently, Wang et al. [29] synthesized 4.5 and 12 nm monodispersed FePt nanoparticles by thermal decomposition of $Fe(CO)_5$ and reduction of $Pt(acac)_2$ in a benzyl ether solvent using oleic acid as a surfactant. Bian et al. [30] obtained single-crystal FePt nanoparticles with a controllable size and isotropic shape using a complex of $Fe(CO)_5$-oleylamine and $Pt(acac)_2$ as the precursors of Fe and Pt, respectively, and adjusting the ratio and temperature of oleylamine and $Fe(CO)_5$.

However, thermal decomposition has the shortcoming of requiring nocuous precursors, such as $Fe(CO)_5$, during

preparation [31]. $Fe(CO)_5$, a metal organic compound with strong volatility, can produce the toxic gas CO during thermal decomposition, which makes the technique difficult to perform and also causes side effects in the composition, particle size, and size distribution of the FePt particles. Therefore, using relatively low-toxicity precursors, such as iron fatty acids, $Fe(acac)_2$ and $Na_2Fe(CO)_4$, to replace $Fe(CO)_5$ has recently attracted considerable interest [1, 31, 32]. Taylor et al. [31] synthesized superparamagnetic FePt nanoparticles (SIPPs) by utilizing a "green" thermal decomposition method. They used iron-fatty acid and $Pt(acac)_2$ as the precursors of Fe and Pt, respectively, octadecene (ODE) or tetracosane (TCA) as solvents, and fatty amine as a ligand. The carbon length of fatty amine ranges from 12 to 18. They compared the effects of fatty amine ligands with different lengths on the composition, uniformity, magnetic properties, shape, and structure of the SIPPs. The results showed that the use of 1-tetradecylamine (TDA) and a 30-min reflux reaction could produce the optimal particles. These TDA-SIPPs exhibited the best properties of saturation magnetization, iron content, monodispersity, and stability and could be a promising MRI contrast agent for cancer detection.

2.2.2. Polyol Reduction Method. Polyol is often used in the preparation of various metal and alloy nanoparticles due to its ability to simultaneously act as a surface active agent, solvent, and reducing agent. The so-called polyol reduction method refers to the use of diol or polyol as a reductant to deacidize a metallic salt to obtain the corresponding nanoparticles. Based on this method, Chou et al. [21] prepared FePt nanoparticles with 3, 6, and 12 nm diameters by heating a reaction mixture of $Pt(acac)_2$, $Fe(CO)_5$, 1,2-hexadecanediol, dioctyl ether, oleylamine, and oleic acid to 297°C and then using ethanol to extract the resultant material. Sahu et al. [33] obtained nanoparticles of diverse sizes with different stoichiometric compositions using an equimolar ratio of an Fe precursor ($Fe(acac)_3$) and Pt precursors ($Pt(acac)_2$, $PtCl_2$, $PtCl_4$, and $H_2PtCl_6{\cdot}H_2O$) and the reducing agent 1,2-hexadecanediol in the presence of octyl ether.

2.2.3. Microemulsion Method. Microemulsions are transparent, isotropic, and thermodynamically stable liquid mixtures that consist of oil, water, surfactant, and cosurfactant. Depending on the ratio of water and oil, microemulsions can be divided into three basic types: the oil dispersed in water type (O/W type), water dispersed in oil type (W/O type), and multiple microemulsion type (W/O/W or O/W/O type). The most commonly used type for MNP preparation is the W/O type microemulsion method (also called the reverse micelle method). The nanoparticles obtained by this method are uniform with a controllable size and stable in a colloid solution. Hyie and Yaacob [34] successfully prepared disordered FCC soft magnetic FePt nanoparticles with 4.7 and 8.4 nm diameters in a water/glycol octyl phenyl ether/cyclohexane (water-in-oil) microemulsion system using $NaBH_4$ as a reducing agent, $FeCl_2$ as the Fe source, and H_2PtCl_6 as the Pt source.

2.2.4. Electrochemical Deposition Method. The electrochemical deposition method is widely used due to its simple equipment requirements and low cost and controllability of the particle properties. Using a single-tank system (relative electrode: Pt tablets; reference electrode: saturated calomel electrode; working electrode: plating conductive layer Si film), Fe/Pt multilayer films were prepared by Leistner et al. [35]. Then, $L1_0$-phase FePt was obtained by heating the multilayer films to 600°C in H_2.

3. Surface Functionalization of FePt Nanoparticles

As a rule, the MNPs for biomedical applications must have high chemical stability, excellent dispersion, and biocompatibility. Therefore, surface modifications, such as ligand additions, ligand exchange, chemical conjugation, and bioconjugation, become necessary. Good surface modification not only can effectively reduce the surface energy needed to obtain MNPs with excellent dispersion but also can improve the biocompatibility of the MNPs. Furthermore, introduction of reactive functional groups to the surface for further conjugation can produce multifunctional nanoparticles. The materials currently used for surface modification of MNPs include organic micromolecular compounds (e.g., 2-amino ethyl mercaptan, aspartic acid, glutamic acid, citric acid, phosphorus acid, vitamin B, and gamma cyclodextrin), organic polymer compounds (e.g., glucose, starch, polyethylene glycol (PEG), polyethyleneimine (PEI), polypeptides, proteins, and polyvinyl alcohol (PVA)), SiO_2, and inorganic nanomaterials (e.g., Au). Among these substances, the characteristics and applications of some materials have been reported in the literature [36–38]. These materials can be attached to the surface of MNPs using ligand addition or ligand exchange [39].

Recently, great progress has been made in the study of FePt nanoparticle surface functionalization. By conducting ligand exchange fromoleic acid to aminoethanethiol (AET), the AET-modified FePt nanoparticles showed excellent water-solubility [40] and no aggregation in stock dispersion [41]. Further bioconjugation with any antibody, peptide, or another nanoparticle can be achieved through ligand exchange. Chou et al. [21] conjugated cysteamine-FePt MNPs with an anti-Her2 antibody and confirmed that the modified nanoparticles for the imaging contrast had excellent biocompatibility and hemocompatibility. Employing cysteamine for ligand exchange, Chen et al. [42] obtained cysteamine surface functionalized FePt nanoparticles (fcc-FePt-A) with good biocompatibility and high chemical stability. Silica and (3-aminopropyl) triethoxysilane were also used in this study to functionalize the surface of FCC FePt nanoparticles. Similarly, the silica-coated and (3-aminopropyl) triethoxysilane surface-functionalized FCC FePt nanoparticles (fcc-FePt-silica-A) showed good biocompatibility and stability.

Using tetraglycol for surface modification, Yang et al. [43] obtained 4 nm FePt nanoparticles that could be engulfed by HeLa cells and cause the T_2 magnetic resonance signal to be significantly decreased.

3-Mercaptopropionic acid (MPA) has been employed to replace the original surfactants on the surface nanoparticles to form nanoparticles with carboxyl groups for further conjugation [44]. Chen et al. [44] used MPA to produce COOH-terminated, water-dispersible FePt nanoparticles. Then, after activating the COOH-FePt nanoparticles with N-ethyl-N 8-(dimethylaminopropyl)-carbodiimide (EDC), folic acid was used to conjugate to the previously produced nanoparticles. The final FePt nanoparticles had excellent biocompatibility and photothermal transduction efficiency.

Using a polyol method, Fuchigami et al. [45] utilized poly (diallyldimethylammonium chloride)- (PDDA-) modified silica particles as a template and produced PDDA-modified silica particles coated with FePt nanoparticles. Subsequently, they dissolved the silica particles in a NaOH solution to obtain FePt-nanoparticles/polycation hybrid capsules, which had a superior capacity to carry drugs and genes.

After introducing poly(L)lysine (PLL) to modify the surface of FePt-folate nanoparticles, PEG, HVGGSSV peptide, and an Alexa fluor 750 fluorescent probe were successively conjugated to nanoparticles by Hariri et al. [46]. This multifunctional nanoparticle had good stability and biocompatibility and could potentially be applied for the radiation-guided targeting and imaging of tumors.

Liu et al. [47] used PEG to functionalize their synthesized FePt@Fe_2O_3 core-shell nanoparticles and conjugated folic acid to the surface of the FePt@Fe_2O_3-PEG nanoparticles. The final products were confirmed to be highly stable in diverse physiological solutions.

4. Biocompatibility and Safety

Good biocompatibility and lack of harm to the human body are prerequisites for FePt nanoparticle applications in clinical practice. The toxicity of FePt nanoparticles is a key factor to consider when estimating their potential in biomedicine. The in vitro cytotoxicity of FePt nanoparticles can be observed in diverse cell lines using colorimetric assays [48], and the kinetics and toxicology can be tested using in vivo animal experiments. In addition, to understand the in vivo toxicity of FePt nanoparticles, precise understanding of the in vivo biodistribution might be crucial.

Chen et al. [42] used an MTS assay to investigate the cytotoxicity of their synthesized fcc-FePt-A nanoparticles in A375M, MCF7, and U2OS cell lines. The result of their biocompatibility study showed that, after undergoing 168 hours of incubation, no cytotoxicity was observed at nanoparticle concentrations below 30 μg/mL.

Chou et al. [21] used an MTT assay, hemolysis test, and biodistribution analysis to evaluate the biocompatibility of their prepared 3, 6, and 12 nm FePt nanoparticles. The results showed no noticeable cytotoxicity (cell viability >90%) at Fe concentrations below 10 mM, and the cell viability was as high as 75% at the highest concentration of nanoparticles (100 mM). No significant hemolysis (<5%) occurred at 0.0001–100 mM Fe concentrations of FePt nanoparticles. Additionally, the biodistribution analysis in 6-week-old male C3H/HeN mice demonstrated that most of the particles were mainly accumulated within the spleen followed by lung and liver and could be gradually removed from the organs with time (approximately one week). Among these three sizes of nanoparticles, the 12 nm FePt nanoparticles displayed the highest serum concentration and circulation half-life. And, the 3 nm-FePt had the highest brain concentration. These results of biocompatibility, hemocompatibility, and biodistribution make FePt nanoparticles potential vectors for in vivo applications.

Liu et al. [47] employed an MTT assay to evaluate the cytotoxicity of FePt@Fe_2O_3-PEG core-shell nanoparticles and the lactate dehydrogenase (LDH) leakage assay to determine the cell membrane integrity. The results revealed no noticeable cytotoxic response in KB cells, even at a high concentration (160 μg/mL), after 3 days of incubation and no clear cell membrane damage induced by the synthesized nanoparticles. Subsequently, they performed studies in mice to observe the potential toxicity of nanoparticles in vivo. For FePt@Fe_2O_3-PEG nanoparticle-treated mice, death and notable abnormalities were absent at the tested dose of 34 mg/kg of Fe for 20 days and no obvious damage, lesion, or inflammation in major organs was observed from Hematoxylin and Eosin (H&E) stained tissue slices. The results of various serum biochemistry analysis showed no notable hepatic toxicity or kidney dysfunction induced by nanoparticles. Compared with the control groups, the hematology analysis was not abnormal. The in vitro and in vivo studies indicated that their synthesized nanoparticles could be a promising multifunctional platform for MRI and targeted drug delivery.

Seemann et al. [49] used the trypan blue exclusion test to evaluate the cell viability of rat cortical astrocytes and applied flow cytometry (FCM) to assess the potential of the nanoparticles to induce apoptosis. The results indicated that the cell viability was not influenced at physiological concentrations of nanoparticles. They concluded that the high degree of biocompatibility, good dispersibility in aqueous solutions, and high magnetic susceptibility at room temperature made these magnetic core-shell nanoparticles potential tools for applications in cancer treatment.

Liang et al. [50] used an MTT assay to evaluate the cytotoxicity of their synthesized FePt-Cys nanoparticles in the ECV304, L929, and HEK293 cell lines. Compared to the control group, no striking differences in cell viability were observed in the FePt-Cys nanoparticle-treated group. After 72 h of treatment with FePt-Cys nanoparticles at a concentration of 100 μg/mL, the viability of ECV304 cells was approximately 110.2%, and no clear decrease in cell viability was observed in L929 cells or HEK293 cells. The good biocompatibility of FePt-Cys nanoparticles was revealed by this study.

Sahu et al. [51] employed an SRB assay to evaluate the cytotoxicity of PEGylated FePt–Fe_3O_4 composite nanoassemblies (CNAs) in the L929 and HeLa cell lines. After 24 h of incubation with CNAs at concentrations of up to 2.0 mg mL^{-1}, low cytotoxicity was observed in L929 cells, and more than 20% of the HeLa cells died. The results demonstrated that CNAs had no effect on cell proliferation of L929 cells but had toxic effects on HeLa cells.

Cytotoxicity studies of FePt nanoparticles that have been previously reported are shown in Table 1.

Table 1: Cytotoxicity studies on FePt nanoparticles.

Material	Fe precursor	Surface coating	NP concentration	Cell line	Test	t (h)	Toxicity	Reference
FePt-SiO_2-A	$Na_2Fe(CO)_4$	SiO_2 shell	200 μg/mL ([Fe]: ~2 μg/mL)	A375M, MCF7, U2OS	MTS	168	V: no loss	[42]
FePt-A	$Na_2Fe(CO)_4$	Cysteamine	30 μg/mL ([Fe]: ~5.3 μg/mL) 60 μg/mL ([Fe]: ~10.5 μg/mL)	A375M, MCF7, U2OS	MTS	168 72	V: no loss V: ~10% loss	[42]
FePt	$Fe(CO)_5$	Cysteamine; conjugated with anti-Her2 antibody	[Fe]: 0.01–100 mM	Vero	MTT	24	V: >90% (below 10 mM); V: 75% (at 100 mM)	[21]
PEGylated FePt@Fe_2O_3	$Fe(CO)_5$	Fe_2O_3 shell, PEG, FA	160 μg/mL	KB, HeLa, HL 7702	MTT LDH	24	No significant cytotoxicity No obvious cell membrane damage	[47]
FePt	$Fe(CO)_5$	Folate-conjugated	5~100 μg/mL	EMT-6	MTT	24, 48	No adverse toxicity effects	[44]
$SiW_{11}O_{39}$-FePt	$C_{10}H_{14}FeO_4$	Silicone-tungsten-oxide	0.015 mg/mL 0.25 mg/mL	Rat cortical brain astrocytes	Trypan blue exclusion, flow-cytometric annexin/PI apoptosis	24	V: 80%, a: 5.4% V: 23%, a: 28.5%	[49]
SiW_xO_y-FePt	$C_9H_9FeO_6$	Hydrophilic SiW_xO_y first shell	0.015 mg/mL 0.25 mg/mL	Rat cortical brain astrocytes	Trypan blue exclusion, flow-cytometric annexin/PI apoptosis	24	V: 81%, a: 7.6% V: 35.7%, a: 26.2%	[49]
FePt-Cys	$FeCl_2 \cdot H_2O$	L-Cysteine	100 μg/mL	ECV304, HEK293, L929	MTT	72	V: ~110.2% (ECV304); V: no obvious decrease (HEK293 or L929)	[50]
PEGylated FePt–Fe_3O_4 composite nanoassemblies (CNAs)	$FeCl_2 \cdot 4H_2O$	Fe_3O_4, PEGylated	2.0 mg mL^{-1}	L929, HeLa	SRB assay	24	Low cytotoxicity to L929; over 20% of HeLa cells died	[51]

NP is nanoparticle; t is the incubation time; [Fe] is the Fe concentration; D is the cell damage; V is the cell viability; a is the cell apoptosis.

5. Biomedical Applications of FePt Nanomaterials

After surface functionalization, FePt nanomaterials have been employed in biosensing, targeted drug delivery, MRI, fluorescence imaging, and therapy experiments. Some biomedical applications of functionalized FePt MNPs are shown in Figure 2.

5.1. FePt Nanoparticles as Contrast Agents in MRI. As a powerful noninvasive medical imaging technique, MRI is extensively used in clinical medicine. Its signal is mainly produced by the protons in the water molecules. By collecting the body's most abundant signal, the water molecule, high-quality soft tissue images, and high-resolution anatomical images can be obtained. Compared with computed tomography (CT) or X-rays, MRI has several advantages, such as no radiation and high spatial resolution. However, the sensitivity of MRI is still low. Therefore, in addition to designing a special pulse sequence, MRI contrast agents must be injected to improve the image contrast and sensitivity. MRI contrast agents are a class of material that can enhance the MRI signal contrast between normal and diseased tissues as well as within normal tissues. According to their different properties, MRI contrast agents are classified into two types: T_1 contrast agents, which mainly shorten the longitudinal relaxation time, and T_2 contrast agents, which mainly shorten the transverse relaxation time. The typical representatives of T_2 contrast agents include some superparamagnetic nanoparticles. Under an external magnetic field, the unpaired electrons spin and generate a local magnetic field, which can shorten the relaxation time of surrounding protons in the water molecules and can effectively shorten the T_2 time [52], resulting in a dark image and negative enhancement effect [53]. The contrast effect can be evaluated by the relaxivity (r_2). A higher r_2 value typically indicates a stronger contrast effect [13].

Due to their superior characteristics, FePt MNPs have recently been one of the hotspots in MRI research. Gao et al. [54] described FePt@Fe_2O_3 core-shell nanoparticles for MR imaging. Compared to MION ($r_2 = 2.778\,(\mu g/mL)^{-1}\,s^{-1}$) and Sinerem ($r_2 = 2.450\,(\mu g/mL)^{-1}\,s^{-1}$), commercial MRI contrast agents, as-synthesized FePt@Fe_2O_3 yolk-shell nanoparticles ($r_2 = 3.462\,(\mu g/mL)^{-1}\,s^{-1}$) exhibited stronger contrast enhancement and could act as a potential MRI contrast agent.

Chen et al. [42] investigated the effectiveness of fcc-FePt-A and fcc-FePt-silica-A nanoparticles as MRI contrast agents. The r_2 values were 887 $mM^{-1}\cdot s^{-1}$ and 210 $mM^{-1}\cdot s^{-1}$ for fcc-FePt-A and fcc-FePt-silica-A nanoparticles, respectively, in the MRI magnetic field (7 T), whereas the r_2 value of commercial Feridex was 148 $mM^{-1}\cdot s^{-1}$. Their work demonstrated that the FePt-based T_2 contrast agents were superior to commercial Feridex with respect to MRI contrast enhancement.

Chou et al. [21] synthesized size-tunable superparamagnetic FePt nanoparticles and investigated their potential as a dual-modality contrast agent for CT/MRI. Their studies showed that superparamagnetic FePt nanoparticles could enhance shortening of the T_2 of proton relaxation and produce efficient CT contrast enhancement. In a further in vivo imaging experiment, selective contrast enhancement of Her2/neu overexpression cancer lesions was achieved in both CT and MRI in tumor-bearing animals injected with nanoparticles.

At 4.7 Tesla, the relaxivities of the SIPPs prepared by Taylor et al. [55] were higher than commercial SPIONs. The relaxivities were 62.2 and 21.37 Hz/mM Fe for SIPPs and SPIONs, respectively. The results indicated that the SIPPs may be superior T_2-weighted MRI contrast agents.

5.2. Fluorescence Imaging Probes. The so-called fluorescent nanoparticles refer to a variety of nanoparticles with fluorescent properties. Fluorescent nanoparticles can be sorted into two types according to the light-emitting principle. One type can emit fluorescence after it is excited by external energy, for example, semiconductor nanocrystals with unique optical and electronic properties, also known as quantum dots (quantum dot, QD). The other type can emit fluorescence after exposure to a labeled fluorescent substance, for example, fluorescent magnetic nanoparticles and quantum dots wrapped silica nanoparticles. Both particles can achieve highly sensitive detection of biological molecules, such as nucleic acids, proteins, and pathogenic microorganisms. Based on the advantages of strong fluorescence emission and antiphotobleaching, fluorescent nanoparticles may also be a promising fluorescence imaging marker.

In recent years, many scholars have prepared fluorescent magnetic nanospheres using FePt nanoparticles. Gu et al. [56] prepared composite nanoparticles containing FePt nanoparticles and amorphous CdS (semiconductor colloids (quantum dots)). These nanoparticles were less than 10 nm in diameter and exhibited good superparamagnetism and fluorescence. Using a one-pot synthesis procedure, Gao et al. [57] obtained superparamagnetic FePt@CdX core-shell nanocrystals (X = S or Se), which could show fluorescence with quantum yields of 2.3–9.7%.

Using the fluorescent dye NOPS to label magnetic FePt core-shell nanoparticles, Seemann and Kuhn [58] observed the fluorescence of these labeled nanoparticles in ethanol (EtOH) and the bright luminescence of the magnetic core-shell nanoparticles (containing labeled and unlabeled particles) with multiphoton excitation (cf. Figure 3). They reported that these bright magnetic core-shell nanoparticles could be employed for in vivo multiphoton imaging in the mouse neocortex as far inward as cortical layer 5.

Taylor et al. [59] encapsulated superparamagnetic FePt nanoparticles with PEGylated phospholipids to generate stealth immunomicelles that could be specifically targeted to human prostate cancer cells and detected by MRI and fluorescence imaging.

These multifunctional FePt nanoparticles with both magnetic and fluorescent properties may be used for multimodal imaging for the diagnosis of diseases.

5.3. Photothermal Therapy. Photothermal therapy is an emerging treatment modality for cancer. By using near-infrared (NIR) light to locally irradiate tumor cells, the light energy can be transformed into heat energy, which can

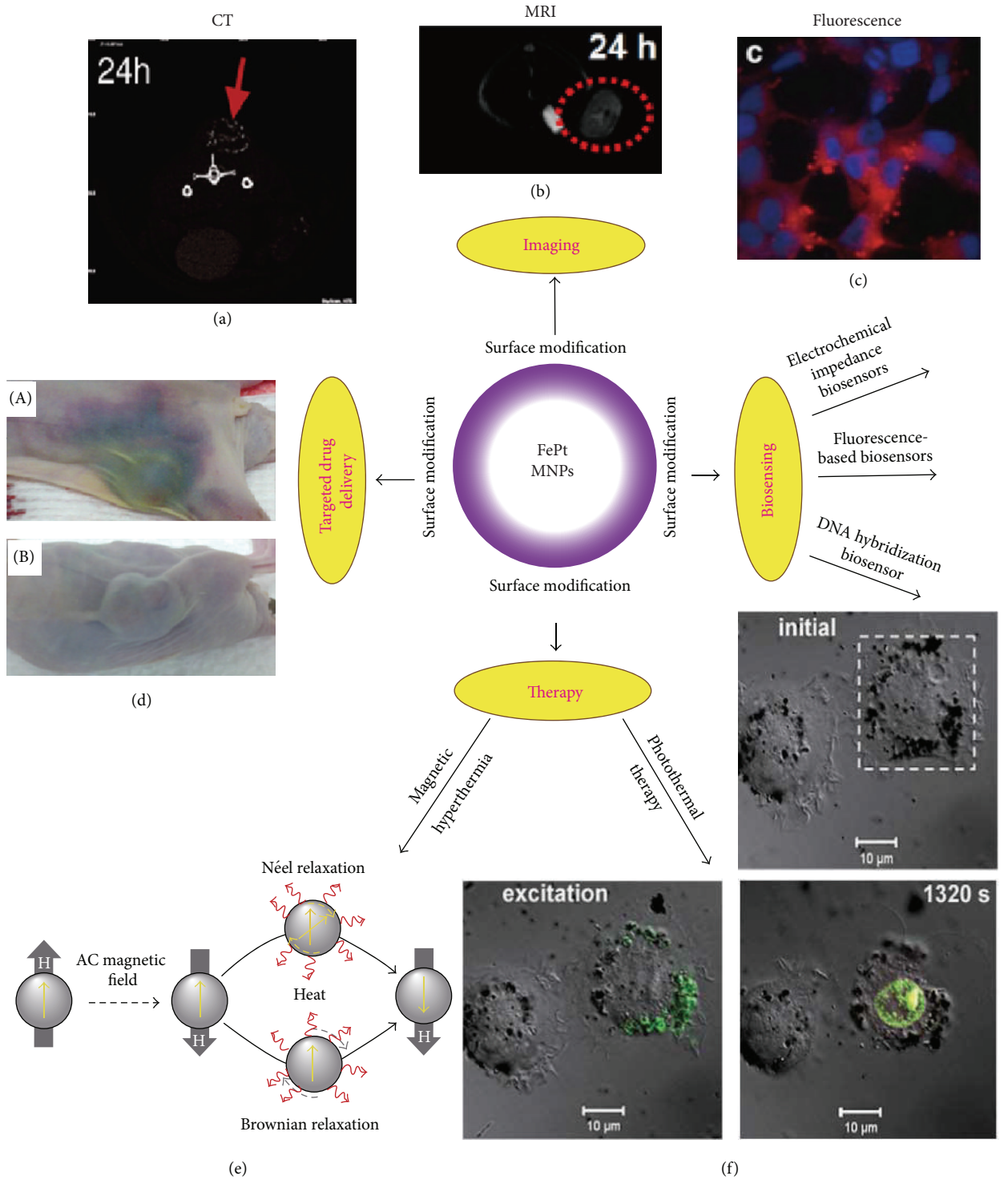

Figure 2: Biomedical applications of functionalized FePt MNPs: (a) a CT image of the MBT2 tumor-bearing mice 24 h after being injected with anti-Her2 antibody-FePt nanoparticles [21]; (b) T_2-weighted MRI of KB tumor-bearing nude mice 24 h after being injected with FePt@Fe_2O_3-PEG-FA nanoparticles [47]; (c) fluorescence image of C4-2 PSMA-positive after 10 min of incubation with J591-DSPE-SIPPs [59]; (d) extensive hematoma around the tumors on PTX alone injected mice (A), no such side effect on mice injected with J591-SPMs (B) [1]; (e) the principle of magnetic heat induction [2]; (f) photothermolysis images of the EMT-6 cancer cell induced by FePt nanoparticles under w10 mJ/cm^2 [44].

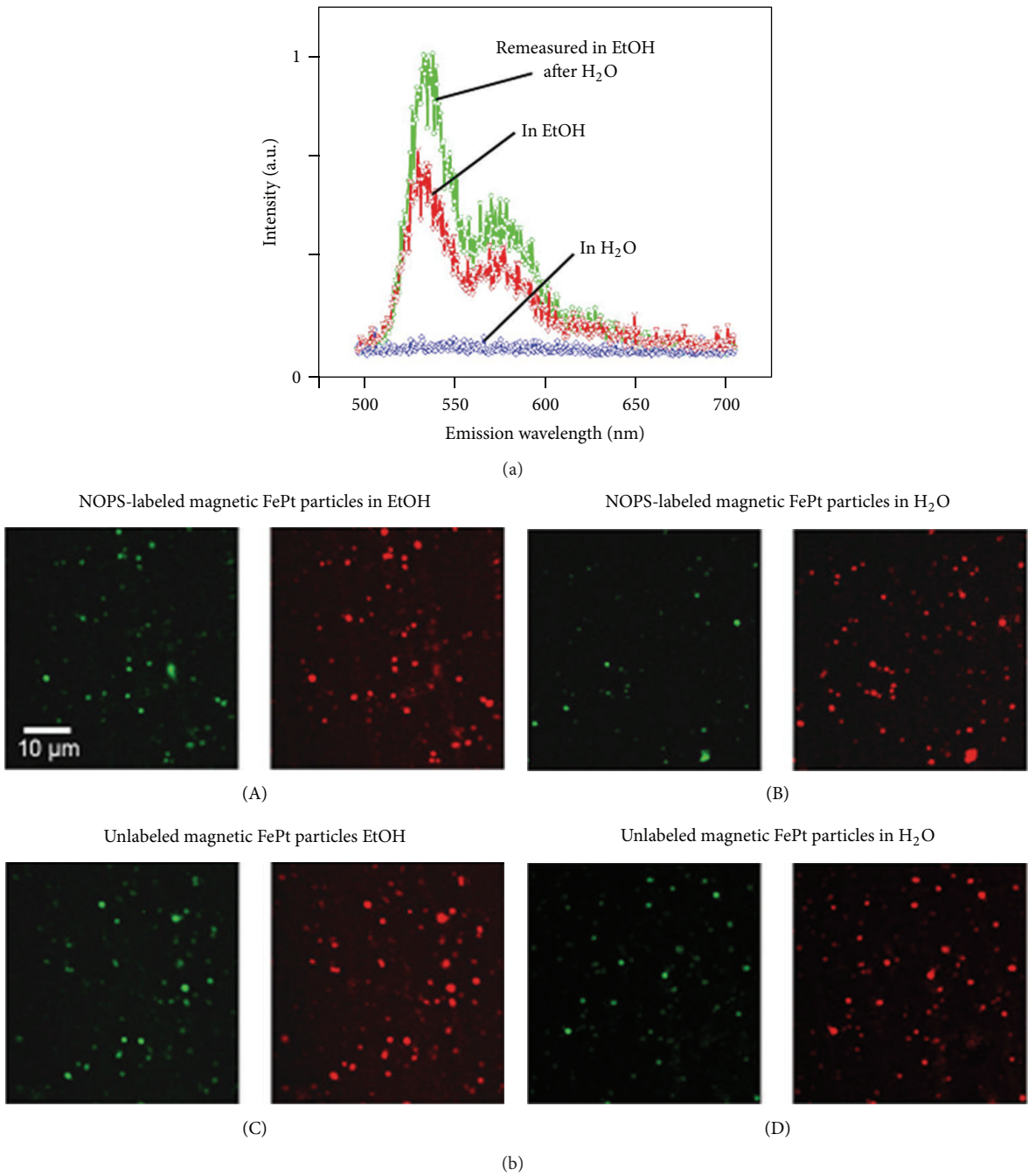

Figure 3: Fluorescence data (a) of the NOPS-labeled FePt nanoparticles (1-photon excitation, wavelength: 488 nm). Bright luminescence (b) of the NOPS-labeled and unlabeled FePt core-shell nanoparticles (multiphoton excitation, two wavelength intervals (green: bandpass 490 nm–560 nm, red: bandpass 570 nm–640 nm)) [58].

degenerate tumor cells and cause necrosis at a certain temperature. Due to the performance of strongly absorbing NIR light, nanometer material can be applied for photothermal treatment of tumor cells after surface functionalization. This process is illustrated in Figure 4 [44].

The photothermal effect of folate functionalized FePt nanoparticles activated by a NIR femtosecond laser has been examined by Chen et al. [44]. Due to their superior photothermal transduction efficiency, these nanoparticles can be heated up to several hundred degrees Celsius in picoseconds under laser irradiation. The threshold laser energy required to damage EMT-6 cells was comparable to that of previously reported gold nanoparticles. These findings suggest various applications for FePt nanoparticles in targeted cancer therapy.

5.4. Magnetic Carriers for Targeted Drug Delivery. MNPs are commonly used as vectors for encapsulated drugs or other therapeutic agents for targeted therapy. After specific target

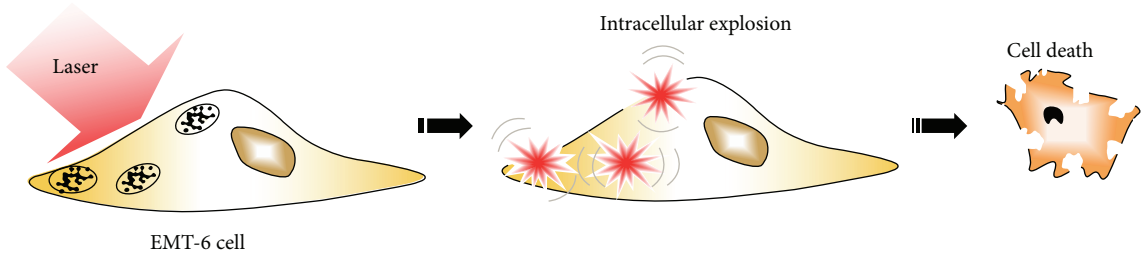

Figure 4: An illustration of photothermolysis of tumor cells mediated by laser-activated MNPs [44].

molecules are conjugated to the surface, these drug-loaded nanoparticles can enter target cells. As a result, targeted drug treatment can be achieved. Taylor and Sillerud [1] encapsulated paclitaxel into SIPPs to produce multifunctional SIPP-PTX micelles (SPMs). Subsequently, they combined SPMs with an antibody against a prostate-specific membrane antigen (PSMA) for the specific targeting, MRI, and therapy of human prostate cancer-bearing mice. The results showed that PSMA-targeted SPMs could effectively prevent C4-2 prostate cancer xenografts from growing in nude mice. In addition, compared to nontargeted SPM-injected and paclitaxel-injected mice, more paclitaxel and platinum was observed in tumors in mice injected with PSMA-targeted SPMs.

Due to the superior magnetic response, MNP carriers may be collected in the lesion under an external magnetic field to achieve targeted drug delivery. Fuchigami et al. [60] performed in vitro application of porous FePt capsules in a magnetically targeted drug delivery system. After the introduction of an anticancer drug and coating with a lipid membrane to avoid leaking of the agents, the magnetic capsules arrived at lung cancer cells and gastric cancer cells within 15 min under a NdFeB magnet (0.2 T), resulting in greater than 70% cancer cell death. As magnetic carriers, FePt magnetic capsules could be effectively utilized for drug delivery systems.

The pH value of tumor interstitial fluid is lower than that of normal tissue. In a low-pH environment, nanoparticles wrapped with pH sensitive lipids can increase the rate of drug release. This is favorable for the application of multifunctional FePt nanomaterials for drug delivery and controlled release [47]. Liu et al. [47] prepared DOX loaded FePt@Fe_2O_3-PEG-FA nanoparticles and incubated them in buffers with pH values of 7.4 and 5.0 to assess their drug release behaviors. After 24 h of incubation, they observed approximately 1.5% DOX release at pH 7.4 and approximately 20% DOX release at pH 5.0, indicating accelerated release at a lower pH value.

5.5. Biosensors. The biosensor is an analytical device that can identify, convert, and detect various substances, such as enzymes, nucleic acids, antibodies, and antigens. Due to their advantages of surface effects, small size effect, quantum size effect, macroscopic quantum tunneling effect, and quantum confinement effect, nanomaterials are attractive prospects for biosensor applications.

Through modification, carbon-decorated FePt nanoparticles have been used as new ultra-high-resolution DNA electrochemical impedance biosensors that can improve the detection of the PML-RARA fusion gene in acute promyelocytic leukemia [61]. Amide ligand-modified FePt/carbon nanotube (CNT) nanocomposite paste electrodes have been employed for the simultaneous determination of tryptophan (Trp), glutathione (GSH), and nicotinamide adenine dinucleotide (NADH) levels [62]. The modified N-(4-hydroxyphenyl)-3, 5-dinitrobenzamide-FePt/CNTs carbon paste electrode can be used as a highly sensitive biosensor to simultaneously determine GSH and piroxicam (PXM) levels [63]. FePt nanoparticles with three different compositions ($Fe_{25}Pt_{75}$, $Fe_{30}Pt_{70}$, and $Fe_{35}Pt_{65}$) displayed higher electrocatalytic activity than Pt nanoparticles for vitamin C electrooxidation [64]. The linear range, sensitivity, and detection limit of the $Fe_{30}Pt_{70}$ NPs/Si nanowire sensors were 0.01–1 mM, 4.347 mA cm^{-2} mM^{-1}, and 0.1 μM ($S/N = 3$), respectively. The sensitivity was more than 10-fold higher than the best performance that has been previously reported for sensor materials (e.g., Pd nanowires: 166.5 μA cm^{-2} mM^{-1}). These FePt nanoparticles could be a superior sensing material for a fast-response vitamin C sensor. Recently, researchers have employed FePt nanoparticles for arsenic detection. Among FePt, FeAu, and FePd nanoparticles, the FePt nanoparticles (detection limit: 1.2 ppb; sensitivity: 1.23 μA ppb^{-1}) showed the best performance and might be an effective, high-performance electrochemical sensor for the detection of ultratrace quantities of arsenic [65].

5.6. Magnetic Fluid Hyperthermia (MFH)/Magnetic Hyperthermia (MH). Using arteriovenous or direct injection, magnetic fluid modified by a specific antibody can selectively penetrate tumor tissue or cells. Under an external alternating magnetic field (AMF), the magnetic fluid in tumor tissue or cells is heated through the main mechanisms of Brownian and Néel relaxation, and then the produced heat kills the tumor. This process is called MFH or MH. This therapy is highly specific; that is, only tissue or cells with MNPs can be heated and killed, whereas the surrounding normal tissues without MNPs are not subject to thermal damage. Simultaneously, this therapy also successfully resolves the difficulty of temperature control in hyperthermia. Generally, tumor cells are more likely to die at temperatures ranging from 39 to 45°C [66]. The MH effect is related to the size, Curie temperature and magnetization of the particles, the intensity and frequency of AMF, and the heat dissipation from the tumor [67].

The use of FePt nanoparticles as a medium for MH has been explored in the last two decades. Marnosono and Saita [66] reported a theoretical assessment of MH using fcc FePt MNPs. These fcc FePt MNPs displayed great superiority to magnetite, maghemite, FeCo, and $L1_0$ FePt MNPs in MH. At $H_0 = 50$ mT and $f = 300$ kHz, the energy dissipation of 9 nm fcc FePt MNPs was $P = 3.97 \times 10^5$ W/m, while the energy dissipation of 19 nm magnetite MNPs was only $P = 1.95 \times 10^5$ W/m.

Seemann et al. [49] successfully demonstrated the magnetocaloric heating effect of as-synthesized tungsten-oxide coated biocompatible FePt core-shell nanoparticles. An approximately 3°C increase in the aqueous suspension was recorded after 15 min in an 831 kHz high-frequency AMF of 250 Gauss field strength (25 mT) at a moderate nanoparticle concentration (0.5 mg/mL).

Hyperthermia combined with ionizing radiation could enhance the tumor damage and thereby enhance the therapeutic effect. Seemann et al. [49] reported that their designed novel nanoparticles had a convenient decay time. Utilization of cold neutrons could activate the content of tungsten atoms in the nanoparticles, resulting in a transformation into the radioisotope W-187, which could provide potentially beneficial 1.3 MeV kinetic energy β-radiation. The specific activity value reached 0.6 MBq/mg. These features make these FePt core-shell nanoparticles promising candidates for advanced radiopharmaceutical applications.

Sahu et al. [51] found that the CNAs with a concentration of 2 mg mL^{-1} could produce a hyperthermic temperature of approximately 43°C. They investigated the MH therapeutic effect of CNAs on HeLa cells. The results demonstrated that approximately 53 ± 2.1% of HeLa cells were alive after treatment with 2 mg mL^{-1} of CNAs in presence of an alternating current magnetic field (ACMF) ($f = 250$ kHz, applied field = 460 Oe), and less than 20% of HeLa cells were alive after incubation with CNAs + DOX in the presence of an ACMF, whereas the control cells without an ACMF showed no obvious decrease in cell viability. Their work showed that DOX loaded CNAs could produce more damage in HeLa cells in hyperthermic conditions.

5.7. Anticancer Agents. Studies have shown that FePt MNPs can suppress the proliferation of some cancer cells. Gao et al. [68] reported that, according to an MTT assay, FePt@CoS_2 yolk-shell nanocrystals showed an IC_{50} of 35.5 ± 4.7 ng of Pt/mL in HeLa cells, which was considerably lower than that of cisplatin (230 ng of Pt/mL). This abnormally high toxicity might suggest that these FePt@CoS_2 yolk-shell nanocrystals could be a new anticancer nanomedicine. Xu et al. [69] reported that FePt nanoparticles functionalized with the *luteinizing hormone-releasing hormone* (*LHRH*) peptide could take precedence in binding to A2780 and suppress the proliferation of these tumor cells. Their work demonstrated that these functionalized FePt nanoparticles could be a new agent for controlled cancer therapy. Sun et al. [70] observed that oleic acid/oleylamine-coated FePt nanoparticles could notably suppress the proliferation of U251, U87, and H4 glioma cell lines in time- and dose-dependent manners. Their work demonstrated that surface-coated FePt nanoparticles could potentially be used as novel therapeutic agents for malignant gliomas.

6. Future Perspectives

Many methods have been used to prepare FePt MNPs. However, the technology used must be further improved to produce FePt nanoparticles to obtain nanoparticles with more controllable and uniform sizes and increased stability. To improve their biocompatibility and application for biomedicine, FePt MNPs require further surface modifications and functionalization with organic functional groups or heterostructures. FePt MNP applications in the biomedical field are increasing and include MRI contrast enhancement, biosensors, and magnetic carriers for targeted drug delivery systems. However, most studies are still in the laboratory phase and far from clinical application. Moreover, the research period has not been sufficiently long to determine the long-term efficacy, toxicity, and metabolism of FePt MNPs in vivo. In addition, other applications in biomedicine, including their use as gene transfer vectors and radionuclide carriers and in MFH, need to be further explored.

However, with further research of FePt MNP technology and the further development of nanomaterial science, larger-scale experimental and clinical studies on FePt MNPs and their application are expected to be conducted, which will play a greater role in biomedicine.

Conflict of Interests

The authors declare that they have no conflict of interests in this work.

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