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Multifunctional nanoparticles: recent progress in cancer therapeutics

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Although much progress has been made in treating cancers, cancer death rates in and around the United States are still high. Current treatments are either ineffective against some cancers or detrimental to patients, which decreases their quality of life. The use of nanotechnology in cancer therapy can potentially increase patient survival, reduce side effects, and reduce mortality rates because nanoparticles (NPs) have the potential to target only tumors and bypass healthy cells. NPs possess many features, including size, shape, charge, and composition, which allow them to carry chemotherapeutics to cancer cells. NPs can also be used in radiotherapy as radiosensitizers and in imaging as contrast agents. Many studies have performed *in vitro* and/or *in vivo* experiments on these particles in human and animal cell lines. This review discusses recent studies on different NPs and their potential use in cancer therapy.

1. Introduction

Cancer is the second-leading cause of death in the United States, surpassed only by heart disease.[1] Even though cancer death rates have been decreasing in the United States for the past several years, cancer is expected to eclipse heart disease within a few years as the number one cause of death.[1] Despite significant advances in the treatment of cancers in recent decades, it is still difficult to eradicate. Many factors contribute to its resiliency, such as its location in the body, the inability of the treatment to reach the tumor cells, and the risk of damaging healthy cells.[2]

Certain cancers, such as pancreatic and brain cancers, reside in vulnerable areas of the body, making them more difficult to treat. The pancreas is positioned near the intestines and the liver, allowing pancreatic tumors to easily metastasize to these organs. Other cancers, such as those located in the brain, are also problematic not only because of the location of the cancerous cells, but also due to the difficulty of delivering the treatment to the malignancies. The brain is protected by a blood–brain barrier (BBB) that restricts the movement of most materials across its boundary.[3] Thus, the BBB makes it more challenging to treat brain cancer with medicine if the drug cannot penetrate the barrier. As a result, specialized medicines and/or treatment techniques are needed to effectively reach and destroy difficult tumors.

Another issue in cancer therapy is that current therapeutics cannot selectively target tumor cells, which can result in damage to healthy cells in the body.[4,5] This can create side effects in patients and possibly cause permanent damage to other tissues. The most common techniques used in these treatments are surgery, radiation, and chemotherapy. In terms of surgery, adverse reactions usually occur where the surgery took place.[6] For example, the surgical removal of oral cancers can permanently affect speech, chewing, swallowing, and other functions related to the mouth depending on where inside the mouth the tumor was located.

Negative responses to radiotherapy and chemotherapy can, like surgery, occur where the tumor is located. However, these treatments can also cause more extensive adverse reactions in the body. Side effects of radiation occurring near the tumor site include skin problems and hair loss at the treatment site, and eating problems when radiation is given to areas of the head, neck, or other parts of the digestive system.[7] Radiation can also result in side effects not associated with the area where the tumor is located, the most common of these being fatigue.

Similar to radiation, chemotherapy can also affect parts of the body near and far from the site of the tumor.[8] Various adverse responses can be induced by chemotherapy depending on the location of tumor, one example being oral mucositis (OM) for oral cancers.[6] The most common universal side effects of chemotherapy are nausea and vomiting. These responses can occur no matter where the tumor is located. Chemotherapy-induced nausea and vomiting (CINV) is activated by chemotherapeutics that trigger various neurotransmitters and receptors that send vomiting stimuli to the central nervous system (CNS). The CNS then sends signals to other organs that induce nausea and vomiting.[9] These and many other unpleasant side effects are some of the downsides to conventional treatment options.

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A novel technique that hopes to eliminate the issues of tumor location, inability of medicine to reach certain malignancies, and risk of damaging healthy cells involves the use of nanotechnology.

2. Properties of nanoparticles

There are a number of criteria that must be met when creating nanoparticles (NPs):

1. The NP must effectively bind and carry the drug(s)
2. The NP must be stable in circulation and biocompatible in the body
3. The NP should preferably have high bioavailability so as to optimize its anticancer effects on tumor cells
4. The NP must be able to target cancer cells while avoiding healthy cells
5. The NP must only release the drug(s) once inside the tumor

These properties can be achieved based on the size, shape, and composition of the NPs. Nanoparticles (NPs), strictly speaking, are defined as materials less than 100 nm and greater than 1 nm in diameter. In nanotechnology, the sizes of NPs are not rigidly bound to these dimensions; occasionally, NPs can be made larger than 100 nm and still be effective. Their size allows them to possess qualities that smaller and larger molecules do not have. NPs are small enough to extravasate due to the leaky blood vessels, and the inefficient lymphatic system of cancer cells prevents the transportation of NPs out of the cells.[10] The ability of NPs to enter tumors and remain inside them is called the enhanced permeability and retention (EPR) effect.[10,11] Furthermore, NPs are large enough that they cannot extravasate normal blood vessels, preventing them from accumulating in other parts of the body that are not being treated.[12] Thus, a balance in the size of nanoparticles is crucial because those that are too small are quickly cleared by the kidneys before they can have an effect on tumor cells, while those that are too big cannot take advantage of the EPR effect.[13,14] Extensive research is being conducted on creating the right nanoparticles for cancer treatment.

In addition to the size of NPs, the ability of NPs to travel through the body undetected is also important for delivering drugs to tumor cells.[15–17] The reticuloendothelial system (RES) consists of macrophages that recognize opsonins – proteins as tag materials for phagocytosis by macrophages – that are attached to particles in the blood stream.[18] Factors that determine how a nanoparticle will interact with the RES include the size, shape, composition of the particle and/or the material that covers it, and the charge on the surface of the particle.[18,19] Therefore, NPs must possess certain characteristics in order to be effective therapeutics in cancer treatment. Many different NPs have been manufactured and tested in different types of cancers, including liposomes, dendrimers, carbon nanotubes, and many more.[20,21] For instance, the possible ways of pancreatic cancer therapy based on the nanoparticles are illustrated in Fig. 1.

3. Nanoparticles used in cancer therapy

Many studies have performed experiments on a multitude of potential nanoparticles, such as liposomes, polymeric micelles,

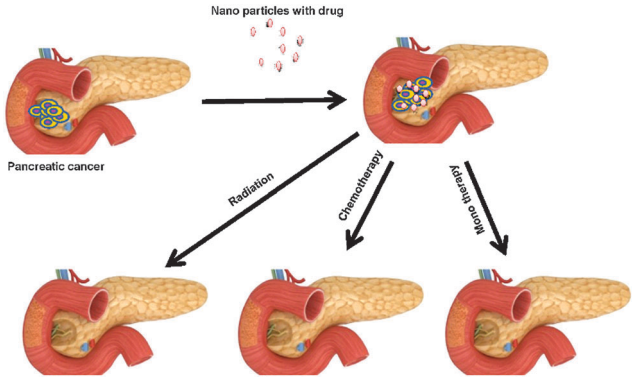

Fig. 1 Schematic illustration of the pancreatic cancer treatment using drug carrying nanparticles. These particles are sensitized and are synergetic or additive to radio or chemo therapy.

and SPIONs, but none of them have shown 100% efficacy in cancer treatment until now. However, a few nanoparticles are approved for cancer clinical trials, summarized in Table 1.

3.1. Liposomes

Liposomes are NPs that self-assembled by utilizing the hydrophobic–hydrophilic interactions between phospholipids and an aqueous solution. The phospholipids form a circular lipid bilayer, where the hydrophilic heads are exposed to water and the hydrophobic tails are directed within the bilayer. The interior of the liposomal core is aqueous, so it can hold water-soluble reagents, while the inside of the bilayer can hold hydrophobic drugs,[20] as shown in Fig. 2. Liposomes are harmless to the body due to their biocompatibility, meaning that they do not produce an adverse reaction in the body.[20] The first NPs used in cancer treatment were liposomes loaded with the chemotherapeutic doxorubicin.[10] The most commonly used liposomal NP is Doxil, which is made from doxorubicin-loaded liposomes modified with polyethylene glycol (PEG).[22]

PEG allows the liposome to travel through the bloodstream without provoking an immune response from the body.[21,23] Doxil is also effective because it is about 100 nm in diameter, so the EPR effect enables it to passively target tumor cells.[21] Doxil was first used to treat Kaposi's sarcoma, but is now used in other cancer types due to its high rate of accumulation in tumor cells compared to doxorubicin alone.[12] One issue with Doxil is that even though PEG enables it to circulate in the blood virtually undetected, PEG also inhibits its uptake into tumor cells because of steric hindrance between the bulky PEG molecule and the surface of the cancer cells.[24] This results in the drug being released from the liposome outside of the tumor cell instead of inside. Accordingly, other liposome-based delivery systems have been designed to avoid this problem.

In addition to being utilized to transport chemotherapeutics like doxorubicin, liposomes can be loaded with other potentially useful anticancer agents. Small interfering RNAs (siRNAs) are short RNA molecules that can destroy mRNA, preventing the mRNA from being transcribed into proteins. SiRNAs are beneficial in treating tumors because they can interfere with

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Table 1 Approved nanoparticles for onco-clinical trials

Year initiated	Description of nanoparticles (NPs)	Cancer targeted by the NPs	Study phase	Sponsor	Clinicaltrials.gov identifier no./others
2014	Paclitaxel polymeric micelles for injectable suspension (other name: genexol PM)	Breast cancer	Not provided	Sorrento Therapeutics, Inc.	NCT02064829
2013	Carbon nanotube based X-ray digital breast tomosynthesis	Breast neoplasms	Not provided	UNC Lineberger Comprehensive Cancer Center	NCT01773850
2009	Auroshell (gold nanoshells)	Locally recurrent breast cancer	Not provided	Nanospectra Biosciences, Inc.	NCT00848042
2014	Fluorescent cRGDY-PEG-Cy5.5-C dots (Silica nanoparticles)	Head, neck melanoma prostate cervical uterine	0	Memorial Sloan Kettering Cancer Center	NCT02106598
2014	Magnetic nanoparticle Injection	Prostate cancer	0	University College London Hospitals	NCT02033447
2014	Dendrimer-enhanced docetaxel (DEP™-Docetaxel)	Breast, prostate, lung and ovarian cancer	1	Starpharma Holdings Limited	Not provided (exclusively in Australia)
2014	Cisplatinum	Pancreatic cancer	1	Roswell Park Cancer Institute	NCT02227940
2014	siRNA-Loaded liposome	Solid tumors multiple myeloma non-Hodgkins lymphoma	1	Dicerna Pharmaceuticals, Inc.	NCT02110563
2014	Liposomal doxorubicin	Head and neck cancer	1	Santa Maria Biotherapeutics	NCT02262455
2012	anti-EGFR immunoliposomes loaded with doxorubicin	Ovarian, fallopian tube, endometrial, solid tumors	1	University Hospital, Basel, Switzerland	NCT01702129
2006	TNF-α bound to colloidal gold nanoparticles	Solid tumors	1	National Institutes of Health Clinical Center (CC)	NCT00356980
2013	Platinum-based albumin-bound paclitaxel (nab-paclitaxel)	Lung cancer	2	Zhejiang University	NCT02016209
2012	Docetaxel-loaded polymeric nanoparticle	Prostate cancer	2	BIND Therapeutics	NCT01812746
2011	Genexol PM	Solid tumors	2	Asan Medical Center	NCT01426126
2014	Superparamagnetic iron oxide (SENTINAC-01)	Bladder and Ureter	3	Hospital Universitari Vall d'Hebron Research Institute	NCT02249208
2012	Paclitaxel polymeric micelles	Breast cancer	3	Nippon Kayaku Co.,Ltd	NCT01644890

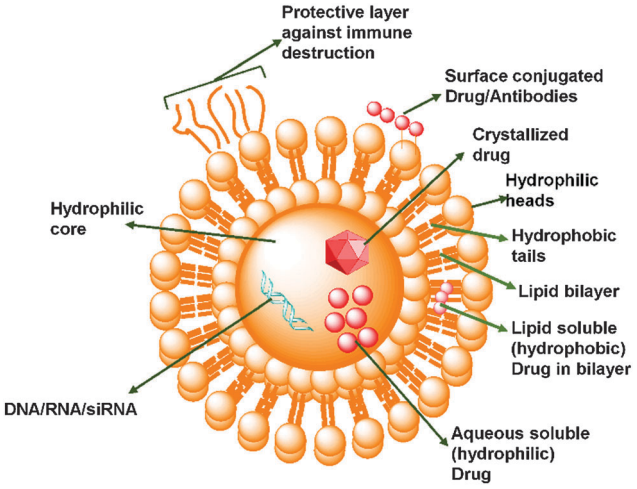

Fig. 2 Schematic illustration of hydrophobic or hydrophilic drug/DNA/RNA/siRNA loaded liposomes.

the expression of proteins produced by the cancer cells. Since siRNA is negatively charged, NPs with positive charges have been designed to carry siRNA due to the electrostatic interactions.[19] However, the immune system recognizes positive charges on materials in the blood and removes them from circulation.[25] Therefore, these carriers need to be coated with a large amount PEG to protect them from the immune system; but, as mentioned earlier, PEG can inhibit the uptake of NPs into tumor cells due to steric hindrance. Thus, Sakurai *et al.*[19] developed a liposome delivery system called a multifunctional envelope-type nanodevice (MEND) that contained the cationic lipid YSK05. The YSK05 requires only a small amount of PEG for protection, enabling the MEND to be taken up by cells more effectively. The investigators found that siRNA accumulation in tumors increased and that mRNA and protein in the target cells decreased.

Liposomes can also be modified by attaching molecules to their surfaces. Liposomes that carry ligand-like molecules on their exteriors have shown promise in targeted cancer therapy due to their ability to actively single out tumors instead of solely depending on the EPR effect to passively enter cancer cells. Aptamer-mediated nanovehicles (AMNVs) have been engineered to actively target different disease markers that are present on cancer cells.[26,27] Aptamers are three-dimensional oligonucleotides that can bend into different formations and bind to specific targets on a cell surface.[26,28] Xing *et al.*[29] used liposomes containing doxorubicin with the DNA aptamer AS1411 on their surfaces to analyze the effectiveness of drug delivery into MCF-7 human breast cancer cells that had been xenografted into naked mice. AS1411 has a high affinity for nucleolin, which is overexpressed on MCF-7 cell surfaces. The investigators found *in vitro* that the AS1411-optimized liposomes showed highly efficient targeting of the MCF-7 cells, as well as increased cytotoxicity of these cells. *In vivo*, they found that the aptamer-modified liposomes showed increased effectiveness in penetrating the MCF-7 tumors. The ability of aptamer-functionalized

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liposomes to target specific markers on cancer cells shows the potential that this technology has in anticancer treatment.

Though aptamers have shown positive results in targeting cancer cells, there are still some limitations. Aptamers tend to dissociate more easily from their receptors than antibodies, as it was found that antibodies have affinities nearly 1000 times higher than those of aptamers.[26] Thus, the relative ease of which an aptamer can disengage from its target prevents the drugs inside of the NPs to which the aptamer is bound from entering the cell. This results in the clearance of the NPs before it can have any effect on the tumor.

As a result of their strong affinities for their targets, antibody-carrying liposomes have also been researched as anticancer treatments. Bandekar *et al.*[30] compared liposomes containing the mouse antihuman prostate-specific membrane antigen (PSMA) J591 antibody to liposomes carrying the A10 PSMA aptamer, with both types of liposomes carrying the radionucleotide ^{225}Ac. Prostate cancer cells express PSMA on their surfaces whereas healthy cells do not. The J591 antibody naturally binds PSMA, while the A10 PSMA aptamer was synthetically engineered to identify PSMA. The researchers found that the J591 antibody was more effective than the A10 aptamer in recognizing PSMA on the tumor cell surface, in entering the cells expressing PSMA, and in killing these cells using ^{225}Ac. The results showed that antibody-carrying liposomes could be effective anticancer treatments due to their strong affinities for specific antigens.

3.1.1. Controlled drug release of liposomes. Although the previous section described how liposomal NPs are able to utilize the EPR effect and actively target tumors, these properties are meaningless if the NPs cannot release their drugs only after entering their target cells. If the medicine leaks out before the NPs reach the tumor, not only will the malignancy be unaffected and continue to grow and reproduce, but the drugs could have negative effects on healthy tissues. Thus, there must be a way to control NPs so that they only release the therapeutic agents after they have entered the tumor cells.

To solve this problem, liposomes are being engineered to trigger drug release when certain changes in the environment occur.[31] However, achieving this specificity in liposomes has been challenging due to the difficulty in making them to only react to changes in the tumor's intracellular environment.[32] Common obstacles that prevent controlled release from liposomes include hydrophilic drugs leaking out into the bloodstream[33] and rapid initial burst release of drugs,[31] although it has been found that liposomes can slowly deliver drugs for a long period of time, possibly after the initial burst.[34] Sometimes liposomes can be externally triggered to release their contents inside cancer cells.[35,36] Subsequent studies focused on liposomal drug release to tumor-area specific or organelle-specific area required in order to improve the therapeutic potential of liposomes.

3.2. Polymeric micelles

Polymeric micelles (PMs) are formed by two or more polymers with different attractions for water. In aqueous solution, the hydrophobic parts of the micelle interact to form the internal core of the micelle while the hydrophilic parts organize around the center and protect it from water,[20] as shown in Fig. 3. PMs are similar to liposomes in that they are formed by hydrophobic and hydrophilic interactions; however, the inner core of PMs is hydrophobic, whereas the inside of liposomes is hydrophilic, clearly shown in Fig. 2 and 3. The hydropathic inner core of PMs allows them to carry drugs that are insoluble in water. PMs also contain the specificity that liposomes are lacking because there is more flexibility in terms of the degree in which their shape, size, and surface can be altered.[22] Another apparent advantage of PMs is that they are usually smaller than liposomes, so they are better suited to take advantage of the EPR effect, which allows them to accumulate inside tumors more easily.[20,37] Some research shows that PMs have short circulation times,[38,39] which would prevent the micelles from having any effect on tumor cells, while other studies suggest that they have relatively long circulation times.[40–42] These discrepancies may be due to the fact that PMs can take different sizes and compositions.

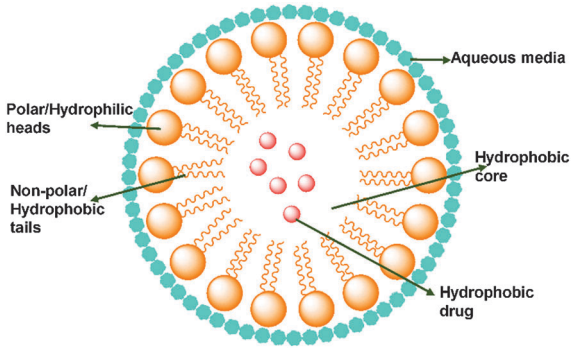

Fig. 3 Schematic illustration of hydrophobic drug loaded polymeric micelles.

There are many different types of PMs that have been researched in preclinical trials. In one study,[37] mice with HT-29 tumor cells were treated with the PM NK012. The NK012 micelle was formed by a copolymer of PEG and polyglutamate (PGlu) that was conjugated to the DNA topoisomerase I inhibitor SN-38. It was found that NK012 was 5.8 times more potent than free SN-38 and cleared more slowly from the tumors, indicating that NK012 was able to passively target tumors through the EPR effect.

Polymeric micelles have been shown to be effective carriers of platinum drugs, another class of chemotherapeutics that have shown promise in cancer therapy. Cisplatin(II) is one of the most common platinum drugs and is often used in combination with paclitaxel.[43] However, patients suffer from side effects because of cisplatin(II)'s cytotoxicity to healthy cells. To eliminate the negative effects of toxic drugs, other biocompatible nanoparticles can be used to safely carry these chemotherapeutics; however, it has often been found that cisplatin(II) is difficult to encapsulate in nanoparticles such as polymeric micelles. Thus, a common way to deliver cisplatin(II) into tumors is to create polymeric micelles containing COOH groups that can bind cisplatin(IV) due to its ability to easily

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interact with the COOH groups. Cisplatin(IV) is the prodrug (*i.e.* inactive) form of cisplatin(II), so it must be converted into cisplatin(II) in order to be effective.

Xiao *et al.*[43] utilized the diblock copolymer MPEG-*b*-P(LA-*co*-MCC-OH) to create polymeric micelles containing cisplatin(IV). They observed that micelle-bound cisplatin(IV) was less cytotoxic than free cisplatin(II), indicating that it is less harmful to healthy cells. They also found that the micelles effectively bound cisplatin(IV) and were able to release it as cisplatin(II) under acidic and reductive conditions that mimicked the intracellular environment. Cisplatin(IV) was also able to chelate 5′ GMP, which simulates the binding ability of cisplatin(II) to the N7 position of guanine and may act to sever the DNA backbone between adjacent guanine compounds. These results show that cisplatin(IV) can be safely carried in the body and could effectively deliver cisplatin(II) to tumor cells while having the same anti-tumor effects as the free version of cisplatin(II).

Another study by Xiao *et al.*[44] found that photosensitive Pt(IV)-azide prodrugs, both free and encapsulated in micelles, were able to release Pt(II) when triggered by UV light. The authors suggested that triggered release is more effective than delivery *via* changes in intracellular pH levels. They also found that the micellar formulations of photosensitive Pt(IV) were taken up more readily by SKOV-3 cells, which were more cytotoxic than other commonly used Pt drugs, and had higher bioavailability than free Pt(IV).

Ma *et al.*[45] used polymeric micelles containing the triblock copolymer mPEG-*b*-PCL-*b*PLL (P, for short) to encapsulate cisplatin(IV). They found that these micelles were thermodynamically stable, more likely to travel to tumors than to healthy areas, and were able to travel inside the nuclei of tumor cells. However, the RES intercepted large quantities of these micelles before they were able to reach their target. Additionally, they incorporated upconversion nanophosphors (UCNPs) into these micelle complexes and showed that UCNPs can convert near infrared (NIR) light to higher energy, which is useful for bioimaging.

The same research group (Xiao *et al.*)[46] was able to encapsulate multinuclear platinum(II) (MNP(II)) drugs instead of platinum(IV) prodrugs by using a negatively charged polymer that interacted with the positively charged MNP(II)s. They found that these micelles released Pt(II) when pH decreased and the Pt(II) compounds were able to form Pt–DNA adducts by chelating with 5′ GMP. Also, micellar Pt(II) entered into HepG-2 cells much more readily than free Pt(II) and cisplatin, which they indicated was likely due to endocytosis of micellar Pt(II) *versus* passive diffusion of Pt(II) and cisplatin. Micellar Pt(II) also showed enhanced tumor growth inhibition and lower system toxicity compared to free Pt(II) and cisplatin. These studies have shown that cisplatin(II) can be effectively delivered to cancer cells *via* micellar cisplatin(IV) without diminishing its anticancer properties.

PMs can also be used to actively target tumor cells. Torchilin *et al.*[47] attached the monoclonal antibody (mAb) 2C5 to PMs made from PEG–phosphatidylethanolamine (PE) conjugates filled with the drug taxol. They injected these targeted micelles into mice with Lewis lung carcinoma (LLC) and compared them to mice injected with free taxol or taxol in non-targeting micelles. The authors also found that the targeted micelles accumulated in LLC 30% better than regular micelles and, compared to both taxol alone and the plain micelles, continued to have the highest concentration levels in LLCs after two hours. These and many other applications of PMs have shown promise in anticancer treatments.

3.2.1. Controlled drug release of PMs. The drug release capabilities of PMs, in addition to their structural properties, make them prime candidates for cancer therapy. Many studies have focused on environmental triggers, such as alterations in pH, for regulation of drug delivery. The sensitivity of PMs to changes in pH can be easily changed due to the many types of polymer compounds that can be used to create PMs.[37,48,49] pH-sensitive PMs can be effective in controlling the delivery of drugs because the pH of human blood is about 7.4, while the pH inside cells can be slightly lower.[37] Moreover, there are also differences in pH between healthy cells and tumors. Therefore, scientists can create PMs with the appropriate pK_as so that they are able to detect fluctuations in pH.

3.3. Dendrimers

Dendrimers are unimolecular, uniformly dispersed polymers consisting of a main core connected to polymer branches that can have different molecules attached to their terminal ends, as shown in Fig. 4. They are less than 15 nm in diameter, making them good candidates for tumor penetration *via* the EPR effect. These structures can carry many different types of anticancer agents due to their symmetrical and highly branched arrangements and the various types of polymer molecules that can be used to create them. A unique property that dendrimers possess is the ability to carry hydrophobic drugs even when they themselves are hydrophilic.

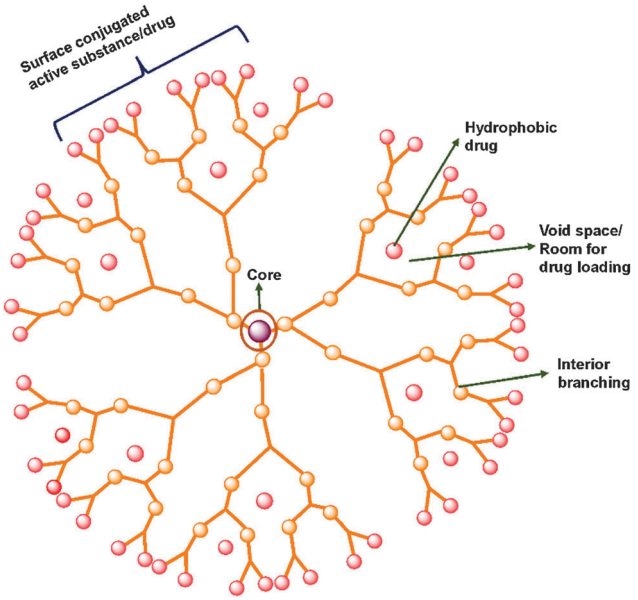

Fig. 4 Schematic illustration of hydrophobic drug loading in different parts of the dendrimer.

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Polyamidoamine (PAMAM) is a biocompatible, water-soluble dendrimer.[50] Even though it is hydrophilic, PAMAM can be used to deliver hydrophobic drugs. This is important because hydropathy is associated with low bioavailability. Patel *et al.*[50] reported that the hydrophobic drugs can be attached to PAMAM's terminal groups or enclosed in the middle of the molecule. They also found that an increase in pH enhanced the solubility of the water-insoluble drug aceclofenac in a PAMAM dendrimer solution which they surmised was due to interactions between the terminal amine groups of the dendrimer and the carboxyl groups of aceclofenac. Another study investigated how PAMAM affects curcumin's anticancer properties against T47D breast tumors.[51] The researchers found that curcumin carried by PAMAM was much more effective against metastasis than curcumin by itself. This is due to PAMAM's hydrophilic nature masking curcumin's low bioavailability.

The flexibility that dendrimers like PAMAM exhibit is also evident in how they can be synthesized to actively target tumor cells. Samuelson *et al.*[52] developed a dendrimer that targets the translocator protein (TSPO) which has been found to be overexpressed in many types of cancers. Another study found that glycosylated dendrimers were 20 to 100 times more cytotoxic against cancer cells *versus* healthy cells.[53] Folic acid added to dendrimer surfaces has shown preference for KB cancer cells that overexpress folate receptors.[53] These and many more surface ligands have shown efficacy in targeted cancer treatment.

3.3.1. Controlled drug release of dendrimers. One of the main issues with using dendrimers is that regulated drug delivery is difficult to achieve. To solve this problem, dendrimer-micelle hybrids have been synthesized to utilize the tumor penetrating abilities of dendrimers and the controlled release capabilities of PMs to make a more effective product. Sunoqrot *et al.*[54] were able to create dendrimer-polymer nanohybrids using fluorescently labeled dendrimers containing folate ligands and PEG-PLA polymers also tagged with a fluorescent label, as shown in Fig. 5. The nanohybrid was able to selectively target folate receptor-expressing KB cells and could effectively release inside the tumor cells. Other studies have created dendrimers that can self-assemble to form micelles.[55] Thus, for the dendrimers to be effective drug carriers, they would have to either be combined with another NP or shaped like other NPs.

3.4. Mesoporous silica nanoparticles

Mesoporous silica nanoparticles (MSNPs) are forms of silica that contain pores that can absorb large amounts of biomaterials. The name "nanoparticle" can be deceiving because MSNPs can be made into either nanospheres or microspheres. Microspheres are about 1000 times larger than the typical NP. The term "nanoparticle" is conventional when discussing either size, but this review will use the word "particle" when discussing both types. Nevertheless, mesoporous silica particles (MSPs) can be made in many different sizes and shapes, survive in harsh environments, and have various pore sizes.[56] The size of a mesoporous silica microsphere (MSM) pore can actually be the same as some NPs or quantum dots (2 to 10 nm), so MSMs can be relatively large. A review highlighted a problem that these particles may be too large to take advantage of

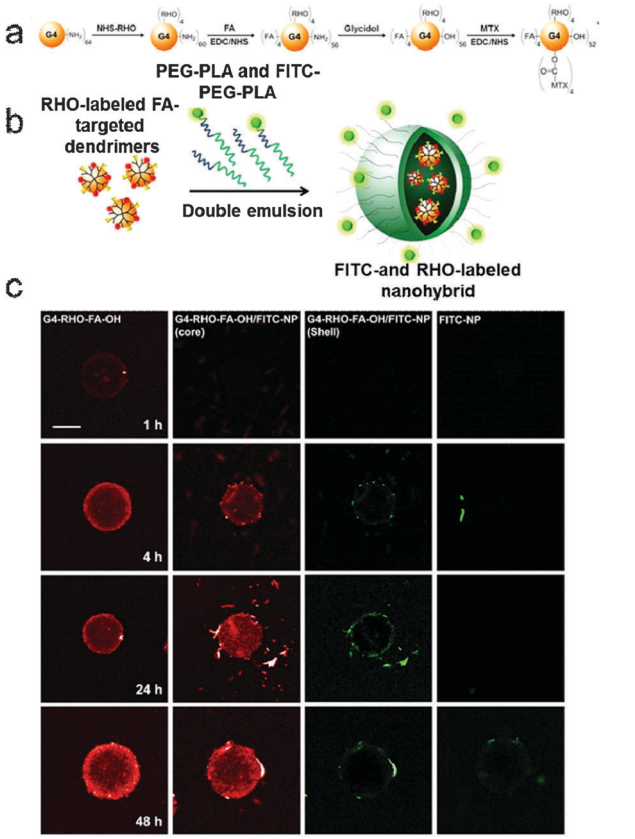

Fig. 5 Overview of nanohybrid preparation. (a) Sequential preparation of the targeted dendrimer conjugates, (b) encapsulation of the dendrimer conjugates into PEG-PLA copolymers to produce the nanohybrids, and (c) CLSM images of KB FR+ MCTS upon incubation with G4-RHO-FA-OH, G4-RHO-FA-OH/FITC-NP, and empty FITC-NPs up to 48 h. Red, RHO-labeled dendrimers; green, FITC-labeled NPs. Images shown were taken at a depth of 80 μm into each spheroid. Scale bar: 100 μm. Image reproduced with permission from ref. 54.

the EPR effect.[56] However, other studies have shown that they are able to effectively carry drugs inside tumor cells.[57] In fact, MCM-41 and SBA-15 are the two most commonly used mesoporous silica particles even though they are microparticles. MSNPs are taken up by cells much in the same way as the previously mentioned NPs. However, unlike other NPs that need ligands attached to them in order to actively target tumor cells, MSNPs sometimes do not need to be coated with a targeting agent because they have high affinities for the head groups of many different phospholipids. As a result, they can enter the cell through endocytosis.[56] Of course, some of these head groups may be found on both cancerous and healthy cells, so targeting agents would have to be used in order to direct the MSNPs only to tumor cells. Chan *et al.*[58] reported that the coated MSNPs integrated with the lanthanide ions europium (Eu) and gadolinium (Gd) (EuGd–MSNPs) with folic acid to target cancer cells expressing the folate receptor. The investigators found that these MSNPs highly targeted folate receptors on cancer cells and also discovered that the hydrophobic anticancer drug camptothecin (CPT) had a higher toxicity in malignant cells when carried by the EuGd–MSNPs. Recently, Dai *et al.*[59] synthesized the novel dendrimer-like MSN (silica nanoparticles with hierarchical pores (HPSNs)) morphologies.

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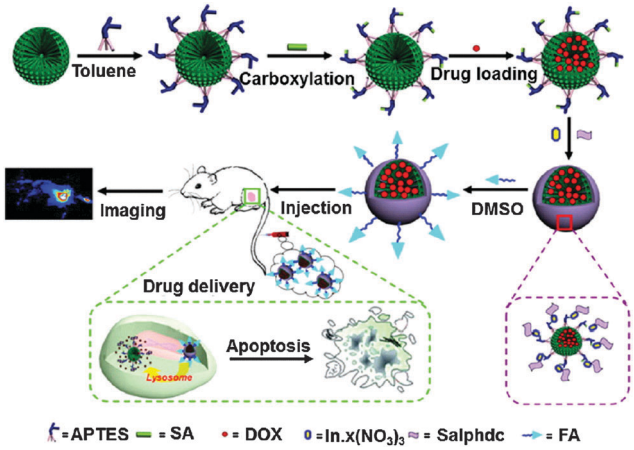

Fig. 6 Construction of pH-responsive HPSN–Salphdc–FA system: drug-loaded HPSN–Salphdc–FA system for tumor therapy and bioimaging *in vivo*. Image reproduced with permission from ref. 59.

The HPSNs were conjugated with and without folic acid and were loaded with the drug DOX. The fabrication of the HPSNs with controlled drug release was shown in Fig. 6. Herein, based on the *in vitro* and *in vivo* studies, the researchers found that the conjugated folic acid was able to distribute doxorubicin to tumor cells based on pH triggers while having little effect on healthy cells. Thus, targeted MSNs are beneficial even though MSNPs by themselves have the ability to interact with the surfaces of cancer cells.

3.4.1. Controlled drug release of MSNPs. MSNPs and MSPs are the most promising nanoparticles in terms of their controlled release abilities. The regulation of drug delivery *via* MSNPs or MSPs is based on the gatekeeping concept, where a molecule will "cap" MSPs until changes in its environment cause the cap detach from the particle, facilitating the release of its contents.[56] For example, there are a variety of NPs that can act as gatekeepers for MSPs, including, but not limited to, coumarin, which is triggered by UV light; PAMAM, stimulated by a reducing agent; and [2]-pseudorotaxane PEI-CD, activated by a change in pH.

3.5. Quantum dots

Quantum dots (QDs) are small fluorescent nanocrystals (2 to 10 nm) with semiconducting properties.[60] They can absorb a broad spectrum of electromagnetic waves and emit light usually in the near infrared (NIR) range. QDs have a central core made of a metal or a metalloid that can be encapsulated by biocompatible molecules, such as ZnS and silica, to prevent QDs from being eliminated from the body before they reach the cancer cells.[61] Due to their optical and electrical properties, they are mainly used as diagnostic agents instead of drug carriers.[62]

Diagnosing cancer involves understanding how a cancer cell utilizes different mechanisms to grow and reproduce. QDs can be extremely helpful in detecting these characteristics due to their fluorescent nature. When QDs are internalized in cells, alterations in the environment can be indicated by a change in the intensity of the fluorescent light emitted or by using different colors for different QDs.[63,64] These techniques allow for the detection of metabolites, proteins, and other biomarkers produced by tumors. Pietilä *et al.*[64] used two types of color-coded QDs attached to cell-internalizing anti-mortalin antibodies in order to investigate how breast cancer cells (BCCs) and human mesenchymal stromal cells (hMSCs) communicate, with the goal being to develop anticancer treatments that target this cross-talk, as shown in Fig. 7. They found that QDs were transferred through direct contact from hMSCs to BCCs, indicating that this transmission possibly includes the movement of mortalin, which is involved in both growth and anti-apoptosis pathways.

QDs can also be helpful in understanding how NPs deliver drugs to tumors.[63] In a study conducted by Chen *et al.*,[65] the liposomal nanoparticle Lipofectamin™ 2000 was transfected with siRNA, and then cultured with QDs. They observed that the QD's fluorescence intensified as the degree of RNA interference increased, indicating that QDs can be used to track the

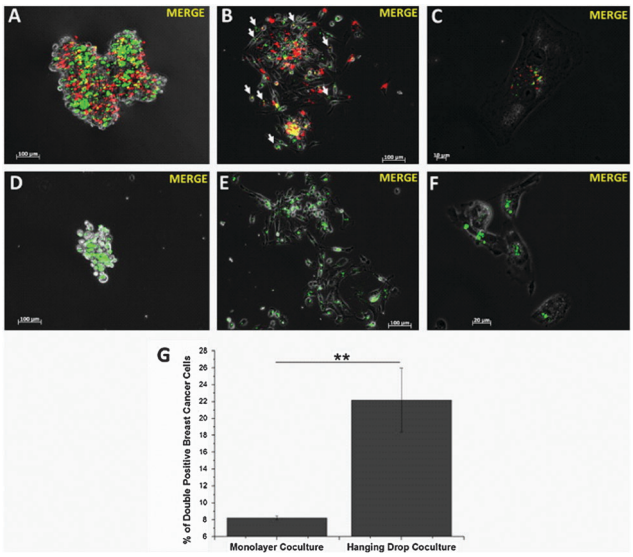

Fig. 7 Hanging drop co-culture induces the intercellular transfer of mortalin bound QDs from hMSCs to BCCs. hMSCs were internalized with mortalin antibody-conjugated QD655 (red) and MDA-MB-231 cells with QD585 (green). hMSCs QD655 and MDA-MB-231 QD585 were seeded into hanging drops in a ratio of 2 : 1 for hMSCs and MDA-MB-231. Hanging drops were cultured for 48 h and then analyzed using a fluorescent microscope. (A) Organosphere formed by hMSCs QD655 and MDA-MB-231 QD585 after 48 h of hanging drop co-culture. (B) Cells start to spread out from the organospheres after 24 h of plating. (C) Double positive MDA-MB-231 QD585 cell after 24 h of plating the organospheres. (D) MDA-MB-231 QD585 grown alone in the hanging drop formed only loose aggregates. (E) After plating the aggregates no double positive MDA-MB-231 QD585 cells were evident. (F) Higher magnification image of MDA-MB-231 QD585 after 24 h of plating the hanging drops. The ratio of double positive MDA-MB-231 QD585 to the total number of MDA-MB-231 QD585 cells was determined after 48 h hanging drop culture following 24 h attachment of organospheres. Four low magnification photographs were taken and results are represented as a mean ± SD of three independent replicates (**$p < 0.01$, two-sample t-test). (G) The % of double positive MDA-MB-231 QD585 cells was significantly higher after hanging drop co-cultures when compared with monolayer co-culture. White arrow indicates a double positive MDA-MB-231 QD585 cell. Image reproduced with permission from ref. 64.

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delivery of drugs by other NPs. As with all NPs, there are limitations in using QDs. It has been reported that water-soluble QDs encapsulated with mercapto-undecanoic acid (MUA) are toxic to healthy cells even in small doses.[66] Tomuleasa *et al.*[21] suggested that the toxicity of QDs may be due to the removal of their coatings in oxidative environments. More research is needed to improve the efficacy of QDs in cancer treatment.

3.6. Superparamagnetic iron oxide nanoparticles

Superparamagnetic iron oxide nanoparticles (SPIONs) are comprised of an iron oxide core that gives them paramagnetic abilities when placed in a magnetic field. This property enables SPIONs to be used not only for drug delivery to tumors, but also as contrast agents in magnetic resonance imaging (MRI). Contrast agents help produce clearer MRI pictures, leading to earlier and more accurate cancer diagnoses.

One SPION that has been extensively researched is ferumoxtran-10. Ferumoxtran-10 is very useful in MRI because of its strong paramagnetic signals at low doses.[10,40] Furthermore, ferumoxtran-10 is lymphotropic, meaning that it has an affinity for lymph nodes.[67] Therefore, it has been utilized in the detection of metastasis of small lymph nodes. One study selected eighty men with resectable (able to be removed by surgery) prostate cancer to undergo MRI with and without ferumoxtran-10.[68] The researchers found that the MRIs using ferumoxtran-10 were much more sensitive and also correctly identified all patients with lymph node metastasis. The MRI images produced by ferumoxtran-10 and other lymphotropic superparamagnetic NPs help "map" the lymph nodes in order to provide a more targeted anticancer treatment.

In addition to their application as contrasting agents, SPIONs can convert energy provided by an alternating magnet into heat that can be used to selectively destroy tumors due to cancer cells being more sensitive to heat than healthy cells.[69] However, the optimization of magnetic NP hyperthermia has not yet been fulfilled. Current studies involve testing SPION accumulation levels in tumor sites and the ability of alternating external magnets to recognize them,[70] while others are using simulation models to test the abilities of various external magnets to enable SPIONs to generate heat.[71] While SPIONs have magnetic properties that allow them to be used as contrast agents and potentially in tumor hyperthermia, they, like many other NPs, can also be utilized for drug delivery. Their iron cores allow them to carry hydrophobic drugs; however, they typically need to be coated with other molecules in order to safely carry drugs through the body. These coating materials often consist of other NPs, such as liposomes and micelles.[72] Iron in low doses is not toxic to the human body, but in imaging and treatment application, iron must accumulate in the affected tissue in order to target cancer therapy to the area.[73] High concentrations of iron in tissue can potentially lead to cytotoxicity of healthy cells, oxidative stress, and DNA destruction with or without cytotoxicity. DNA damage in the absence of cytotoxicity can lead to the formation of new cancer cells and/or cause permanent damage in progeny. As a result, recent studies have focused on creating SPIONs that are safe for the human body. Many studies have investigated how coatings can eliminate the toxicity of SPIONs, with the majority of these studies finding that toxicity of SPIONs encapsulated with various coatings occurs at levels above 100 μg ml^{-1}.[73] More research needs to be done to determine the efficacy of SPION-based cancer treatment.

3.6.1. Controlled drug release of SPIONs. Hyperthermia generated by an external magnet can trigger the release of chemotherapeutics.[31] Of course, this mechanism would have to be activated after the SPION enters the tumor. Hyperthermia can control drug delivery through bond breaking or enhanced permeability.[74] The bond breaking mechanism dissociates the drug from the surface of SPIONs, while the enhanced permeability process occurs when the SPION is encapsulated by a polymeric nanoparticle. Overall, the control of drug delivery depends on how the magnetic field is delivered and the type of electromagnetic waves used to create the field.[74]

3.7. Carbon nanotubes

Carbon nanotubes (CNTs) are made of graphite sheets rolled into cylinders. Unlike liposomes, polymeric micelles, and dendrimers CNTs have electrical, chemical, physical, and other properties that allow them to be used in other areas of cancer therapy besides drug delivery. One of their biggest assets is that they can be used as biosensors. Biosensors distinguish metabolic activity between different cell types by detecting changes in electrical potential that result from alterations in electrochemical gradients, ion movement, and other biological processes. One study engineered multi-walled carbon nanotubes (MWCNTs) made of concentric layers of single-walled carbon nanotubes to detect biomarkers associated with the surrounding environments of MGC-803 gastric cancer cells and healthy GES-1 gastric mucosa cells.[75] The MWCNTs contained an Au–Ag alloy covering. Volatile organic compounds (VOCs) released by MGC-803 during metabolism interact with the Au–Ag coating, producing electrochemical signals. Using an *in vitro* setup, the investigators were able to use gas chromatography coupled with mass spectrometry (GC-MS) to discover metabolites that were found only in MGC-803 cells, in both MGC_801 and GES-1 cells, and only in GES-1 cells.

Other studies have used CNTs to not only detect metabolites produced by cancer cells, but to also actively single out tumor cells. Madani *et al.*[76] constructed a single-walled carbon nanotube (SWCNT) that targeted human breast cancer cells. CNTs have low solubility, resulting in low bioavailability. As such, the researchers functionalized the naked SWNCTs with strong acids to increase their absorption in the body. They then attached fluorescence labeled lectin – which was derived from *Helix pomatia* agglutinin – to the surface of the SWCNT because of its ability to detect alterations in protein glycosylation, a process that is common in metastatic tumors. The researchers incubated both free lectin and lectin attached to SWNCTs with MCF-7 breast cancer cells and, by measuring the intensity of the fluorescent lectin, found that the SWNCT-attached lectin proteins were more prominent in the tumors than the free lectin.

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Along with their use as biosensors, CNTs can be used for drug delivery like the previously described NPs. Using an *in vitro* setup, Mody *et al.*[77] sought to compare liposomes, dendrimers, and MWCNTs in their abilities to carry and deliver the chemotherapeutic docetaxel. They found that MWCNTs encapsulated with carboxylate ions were able to capture and release more docetaxel than the other NPs.

In spite of the many unique properties that CNTs exhibit, these characteristics are difficult to be utilized in cancer therapy due to the low solubility of CNTs in water.[76] As described earlier in the discussion of SWNCTs, CNTs must be functionalized in order to increase their bioavailability. However, encapsulating CNTs with certain materials, such as those that covalently bond with the carbon in CNTs,[76] can mask their electrochemical characteristics.

3.7.1. Controlled drug release of CNTs. Many controlled release mechanisms use the electrical properties of CNTs to regulate drug delivery. Miyako *et al.*[78] engineered a PEG-PL liposomal-SWCNT "nanotrain" containing fluorescent dye that they could maneuver through a microchannel *via* an electrical potential gradient. They then used an NIR laser to control the release of the dye. This experiment, and ones like it, would have to be tested again using actual therapeutics – and preferably *in vivo*– in order to determine if this technology can be used in humans. Another *in vitro* study pretreated MWCNTs with an electrode coating.[79] This coating had little electrical impedance, allowing the researchers to more easily control the release of the drug from the NPs.

3.8. Gold nanoparticles

Gold nanoparticles (AuNPs) have recently been discovered as possibly all-encompassing materials in cancer treatments. While the aforementioned NPs may only have drug carrying and/or imaging capabilities, AuNPs possess optical, electrical, physical, and chemical properties that enhance their anticancer abilities.[80] Another advantage of using AuNPs is that they are also biocompatible, so they are safe inside the body.[80,81] With these properties, AuNPs can potentially be more effective anticancer agents than other NPs.

Au possesses optical properties that allow it to absorb light rays, generating heat that can be used to either by itself to destroy cancer cells or eradicate tumors in conjunction with chemotherapy or radiation. A technique called thermal ablation uses NIR rays to heat tumor cells in order to induce apoptosis. NIR therapy is not considered radiotherapy because infrared light is not a high-energy ionizing ray like gamma and X-rays. The efficacy of thermal ablation has been challenged due to the tendency of heat generation by the NIR laser to disperse before reaching the tumor. Researchers have proposed using the light absorbing properties of AuNPs to concentrate the heat from the NIR laser onto the tumor cells. Several studies have investigated the use of AuNPs for NIR thermal ablation in breast cancers.[82,83] One study showed that SK-BR-3 breast cancer tumors containing AuNPs had a lower survival rate when treated with an NIR laser than those that were not incubated with AuNPs.[81] Another experiment involving SK-BR-3 cancer cells showed that AuNPs attached to a human epidermal growth factor receptor 2 (HER-2) antibody and PEG were more effective at entering and destroying tumor cells after NIR laser treatment than AuNPs not containing either reagent.

As previously stated, the heat generated from AuNPs treated with a NIR laser can be used in conjunction with chemotherapy drugs to effectively kill tumor cells. One study showed that doxorubicin-containing AuNPs stimulated with a NIR laser were more cytotoxic than free doxorubicin, liposomal doxorubicin, and AuNPs not treated with NIR light.[84] In this experiment, the investigators wanted to use chemotherapy and the optical properties of hollow gold nanospheres (HAuNSs) to effectively kill breast and ovarian tumors. The HAuNSs were filled with doxorubicin and coated with PEG; they named this entire complex NP3. *In vivo*, it was found that NP3 plus the NIR laser treatment was more effective at destroying tumors than free doxorubicin, liposomal doxorubicin, and NP3 not treated with the NIR laser.[84] The enhanced effectiveness of the NP3-plus-laser treatment was due to the increased efficiency of thermal ablation as a result of absorption of NIR light by HAuNS, combined with the chemotherapeutic effects of doxorubicin released from NP3. Thus, the optical properties of AuNPs help make them more effective than other NPs against tumor cells and augment the efficacy of thermal ablation.

Even though thermal ablation using AuNPs has shown positive results, there is still a risk of affecting healthy cells if the AuNPs do not actively target tumor cells. As such, studies have created modified AuNPs to actively single out certain markers on tumor cells. One structure that can be targeted that is commonly overexpressed on tumor cells is the transferrin (Tf) receptor. This receptor participates in cell proliferation pathways that allow tumors to grow and divide rapidly.[81] Wiley *et al.* discovered that AuNPs covered in the Tf were able to cross the BBB.[85] The researchers found that AuNPs of 45 nm and 80 nm in diameter were able to reach the brain parenchyma (the functional part of the brain), as shown in Fig. 8. The extent of their accumulation inside the parenchyma depended on the amount of Tf on their surfaces. These results can play a crucial role in the creation of AuNPs that can effectively deliver chemotherapeutics to hard-to-reach brain cancers.

In addition to utilizing of the unique properties of Au in conjunction with chemotherapy, these characteristics can also be used with radiotherapy. AuNPs can be utilized as radiosensitizers and contrast agents due to Au's high atomic number.[86,87] Radiosensitizers can enhance the dose of radiation in tumor cells by sensitizing the cells to radiation. One of the first studies[81] to use AuNPs to improve radiation found that in mice with EMT-6 mammary carcinomas, the mice injected with AuNPs two minutes before radiation treatment had a higher one-year survival rate than mice treated only with radiation. Jain *et al.*[88] irradiated mice either with AuNPs or without AuNPs that were injected five before the radiation was given. The results showed that radiation alone delayed tumor growth, but radiation combined with AuNPs resulted in a large reduction in tumor growth a month after treatment. These findings suggest that the ability of gold to absorb the high-energy rays augments the effect of radiation on tumor cells.

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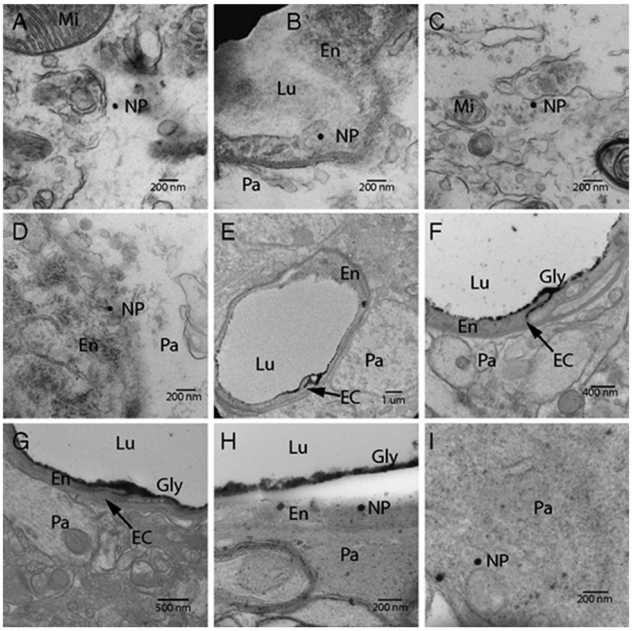

Fig. 8 TEM images of AuNPs in the brain. Mi, mitochondria; Lu, lumen; En, endothelial cell; Pa, parenchyma; EC, endothelial cleft; NP, nanoparticle; and Gly, glycocalyx. (A) 80 nm, 20-Tf nanoparticle in the parenchyma. (B) 80 nm, 20-Tf nanoparticle inside a vesicle of a BBB endothelial cell. (C) 80 nm, 200-Tf nanoparticles in the parenchyma. (D) 80 nm, 200-Tf nanoparticle near the basal surface of an endothelial cell. (E) Perfusion fixation with lanthanum nitrate showing lanthanum penetrating the inter-endothelial cleft with no subendothelial staining. (F and G) Injection of 80 nm particles, followed by perfusion fixation at 8 h postinjection. Neither the 20-Tf/Au formulation (F) nor the 200-Tf/Au formulation (G) degrades the BBB tight junctions to lanthanum nitrate; the same interendothelial cleft penetration with no subendothelial staining is seen. (H) 80 nm, 200-Tf particle inside and near the apical surface of the endothelial cell. (Note that the lanthanum nitrate-stained glycocalyx separated from the cell surface owing to the electron beam during imaging.) (I) 80 nm, 200-Tf particle found within the brain parenchyma after perfusion fixation. Image reproduced with permission from ref. 85.

Besides acting as radiosensitizers, AuNPs can also be used as contrasting agents. These materials help provide a higher definition of tumors to allow for more accurate diagnoses.[88] Compared to iodine, the most commonly used contrasting agent, AuNPs were found to produce better contrast at energies above 80 keV.[88] AuNPs were also found to be retained longer than iodine inside EMT-6 breast tumors when observed with a mammography unit from two minutes to 24 hours after injection.

AuNPs also have the potential to be useful in functional imaging. Historically, computerized tomography (CT) scans have only been used to observe the structure and not the activity of tumors because of iodine's inability to attach to molecular proteins. This is an issue because understanding how tumors operate and survive is important in curing cancer. In an *in vitro* study, AuNPs were conjugated to UM-A9 antibodies, which attach to A9 proteins that are commonly over-expressed in head and neck cancers.[88] The A9 protein is involved in the pathway controlling metastasis. It was found that the UM-A9-conjugated AuNPs absorbed more radiation in cells expressing A9 proteins than in tumors that did not. This suggests that modified AuNPs can be used in CT scans for functional imaging due to their ability to bind proteins expressed by cancer cells.

3.8.1. Controlled drug release of AuNPs. Au has many features that can be utilized for controlled drug release, but most research seems to focus on how Au's optical properties can be used for hyperthermia, which can then be used to release drugs within tumors at the appropriate time. One study used an Au nanocage containing doxorubicin, which was covered with a polymer to absorb NIR light.[89] The absorption of the light caused the polymer to collapse, releasing the doxorubicin. Another study used peptide-coated Au nanoshells loaded with siRNA to observe how NIR light affected the delivery of siRNA to tumor cells.[90] The investigators found that using NIR light to trigger Au nanoshells to release their contents resulted in the down regulation of a green fluorescent protein (GFP) expressed in human lung H1299 cancer cells.

3.9. Other nanoparticles used in cancer therapy

In addition to the previously discussed NPs, many other NPs have been studied extensively in cancer research, with varying success. Nanoemulsions are usually formed using oil-in-water (O/W) or water-in-oil (W/O) techniques, with O/W being the most common of the two methods (Lu *et al.* 2012).[91,92] The droplets that form (oil droplets in O/W and water droplets in W/O) when the two immiscible liquids are mixed are typically 20 to 200 nm in size.[92] Nanoemulsions have been shown to carry poorly water-soluble drugs, thus increasing their bioavailability. Wu *et al.*[93] created a self-microemulsifying drug delivery system (SMEDDS) that increased the relative oral bioavailability of curcumin by 1213% and fully released curcumin at 10 minutes.

Nanoemulsions can also be utilized in bioimaging. Balducci *et al.*[94] created a perfluorocarbon (PFC)-based nanoemulsion with an NIR probe (PFC-NIR) for detecting inflammation. They reported that it had been previously found that PCF nanoemulsions could be used as contrast agents in MRI to image inflammation. By adding an NIR probe to the PCF emulsions, they were able to improve the imaging quality of inflammation that occurred *in vivo*. Disadvantages of nanoemulsions include the lack of controlled release.

Protein nanoparticles, particularly those composed of albumin, have also shown great potential in cancer therapy. In 2005, the FDA approved Abraxane® (ABI-007), which is composed of albumin-bound paclitaxel, for metastatic breast cancer.[95] Desai *et al.*[96] found that ABI-007 had a maximum tolerated dose of 30 mg kg^{-1} d^{-1} *versus* 13.4 mg kg^{-1} d^{-1} for Cremophor-based paxclitaxel, and aggregated inside tumors 33% more than Cremaphor-bound paxclitaxel at equal doses. A phase III clinical trial conducted by Gradishar *et al.*[97] found that ABI-007 had higher response rates, had longer tumor progression time, and reduced incidence of grade 4 neutropenia compared to traditional paclitaxel in women with breast cancer.

Other protein NPs includes amphiphilic peptide NPs that carry antibodies. Protein NP-bound IgG antibodies have been

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observed to be retained in 4T1 mouse mammary tumors for up to 120 hours *versus* only 24 hours for free IgG antibodies.[98] They also retain their biological activity even when bound to the amphiphilic peptide. These NPs are potentially useful for targeting biomarkers on the surfaces of cancer cells.

Nanofibers are another class of NPs. They can be inorganic, organic, or a mixture of the two materials (Díaz *et al.* 2013) and are typically less than 1000 nm in diameter and vary from tens of nanometers to a few microns in length (Lee *et al.* 2015).[99,100] Their large surface areas, low density, and high pore volume allow them to load large amounts of drugs (Díaz *et al.* 2013).[99] Xu *et al.*[101] showed that BCNU-loaded organic nanofibers were more effective against rat Glioma C6 cells than free BCNU. Kim *et al.*[102] engineered a smart hyperthermia nanofiber consisting of magnetic nanoparticles (NPs) that could be turned 'on' or 'off' using an alternating magnetic field (AMF). When turned 'on', the nanofibers were triggered to release their contents (doxorubicin), resulting in the death of 70% of the human melanoma cells in the experiment. Despite these promising results, not many studies have been done on nanofibers in cancer therapy.

4. Future perspectives

Innovation in cancer treatment is key to improving the health outcomes of patients. NPs have been shown to be novel anticancer drug carriers that can potentially outpace current cancer therapies. In chemotherapy, NPs can improve the biocompatibility, bioavailability, selectivity, and release kinetics of chemotherapeutics, making them more effective against tumors and less harmful to healthy cells. In radiation therapy, NPs can be employed as radiosensitizers that aggregate within malignancies to sensitize these cells to radiation. Additionally, NPs can act as bioimaging agents and can destroy cancer cells without the simultaneous use of chemotherapeutics and/or radiation *via* novel techniques, such as hyperthermia.

Despite these qualities, challenges remain, particularly in engineering NPs that will make it through all four clinical trial phases. The FDA approval rate for all oncology drugs is only around 5% and is estimated to be even lower for NP cancer drugs due to obstacles that more traditional cancer drugs do not face. For example, it is more difficult to demonstrate the potential success of an NP drug when there are so few on the market. To alleviate this issue, the Nanotechnology Characterization Laboratory (NCL) has provided protocols for a number of tests (found at http://ncl.cancer.gov/working_assay-cascade.asp) that they will perform in order to determine if NPs tested in preclinical studies are acceptable for phase I clinical trials. The NCL provides this service for free, but researchers must go through a two-part application process for their NP to be (http://ncl.cancer.gov/working_application-process.asp) accepted. The steps that must be taken by researchers to get NPs through preclinical and clinical trials can take years and are expensive to complete, making it difficult to establish NPs in the cancer therapeutic market.

Despite these hurdles, NPs have the potential to greatly improve cancer outcomes. Their ability to target cancer cells while avoiding healthy tissues will increase survival rates and patient compliance. They also have the ability to eliminate short- and long-term side effects, providing an improved quality of life for cancer patients. Hopefully, these features will ultimately lead to more safe and effective NP drugs that will be approved for clinical use.

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