

Phenylboronic-acid-based Functional Chemical Materials for Fluorescence Imaging and Tumor Therapy

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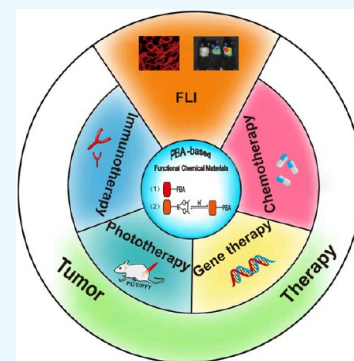
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ABSTRACT: Various functional chemical materials have been widely used in imaging and tumor therapy. Targeted ligands such as antibodies, peptides, and small molecules have been combined with functional materials to enhance cellular uptake and are used for active targeting of cancer cells and tumors. Among them, phenylboronic acid (PBA), as a small molecular ligand, has the characteristics of low cytotoxicity and easy modification. PBA improves the cancer cell imaging and tumor treatment effect by binding to glycans on the surface of cancer cells. In this Mini-Review, we introduced the modification strategy and targeting strategy of PBA. We focused on the applications of PBA-based functional materials in fluorescence imaging and tumor therapy. For fluorescence imaging, the potential of PBA-based functional chemical materials in cancer diagnosis and tumor targeting was proved by cell imaging and *in vivo* imaging. For tumor therapy, we mainly discussed the applications of PBA-based functional chemical materials in chemotherapy, gene therapy, phototherapy, and immunotherapy. PBA-based functional chemical materials provide a useful method for cancer diagnosis and treatment.



1. INTRODUCTION

Cancer is one of the major diseases threatening human health. In the context of a high incidence of cancer, targeting imaging and therapy of tumors are of great significance to the diagnosis and treatment of cancer. Commonly used imaging techniques now include magnetic resonance imaging (MRI), computer tomography (CT) imaging, positron emission tomography (PET) imaging, ultrasound (US) imaging, photoacoustic imaging, fluorescence imaging (FLI), and so on. The use of these imaging techniques can detect tumor sites in real time. Compared with other imaging technologies, FLI uses targeting fluorescent probes to specifically bind to overexpressed receptor molecules on the tumor surface, achieving imaging of the tumors. FLI can be used to distinguish tumors from normal tissues and has better specificity and sensitivity. In addition, the emergence of targeted strategies also reduces the damage of drugs to normal cells and tissues, realizing tumor-specific treatment. At present, a simple method for enhancing the specific targeting ability of functional materials is to combine the materials with targeting ligands. Commonly used targeting ligands include antibodies, peptides, and some small molecules. Among them, small molecules refer to receptor ligands with specificity for cell surface receptors and transport proteins. The binding affinity of small molecules to the receptors is lower than other ligands, and the weak binding ability between small molecules and receptor ligands may be more favorable for transcytosis and tissue penetration.¹ Because the strong binding effect may cause the materials to be trapped in the tissue or transported to the lysosome, it is

not conducive to the penetration of the material in the tumor tissue and the realization of efficient tumor treatment. As an important receptor ligand, phenylboronic acid (PBA) has the advantages of low cost, high stability, small size, low immune response, and easy chemical modification. Due to these characteristics of PBA, the materials functionalized with PBA have universal usages in the biological field. Edwards and co-workers first explored the binding ability of boric acid to diol-like structures at different pH values in 1959, which helped to study the binding of PBA to saccharides.² PBA-based functional materials can react with diol-like structures to generate reversible borate esters, which were mainly used for saccharide sensing in the early stage. With the development of biomedicine, glycoprotein overexpression on the cancer cell surface has been found. PBA-based functional chemical materials have been developed in glycoprotein detection, cell imaging, drug delivery, and other biological applications. In 2013, PBA-based functional chemical materials were explored to bind with sialic acid (SA) on the surface of cancer cells. PBA achieved tumor-targeted imaging *in vivo*. PBA and the diol structure of SA can form the reversible borate, which promotes

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the uptake of PBA-based functional chemical materials by cancerous cells. These findings open up new approaches for the design of tumor-specific probes. Combining PBA with fluorophores can achieve selective imaging of cancerous cells overexpressing SA. The combination of PBA and nanocarriers realizes the effective delivery of therapeutic agents, which increases the accumulation of therapeutic agents at tumor sites and improves tumor treatment effects. Therefore, PBA provides a chemical functional group to guide the therapeutic agents and nanodrugs into the cancerous cells and tumors.

In the Mini-Review, the modification of PBA on functional materials and the targeting strategy of PBA-based functional materials are introduced. We mainly summarize the recent applications of PBA-based functional materials in fluorescence imaging and tumor therapy, which include: (1) FLI of PBA-based functional materials in cancer cells and tumors and (2) the applications of PBA-based functional chemical materials in chemotherapy, gene therapy, phototherapy, and immunotherapy. We also have an outlook on the prospect of PBA-based functional chemical materials in cancer treatment.

2. MODIFICATION OF PBA ON FUNCTIONAL CHEMICAL MATERIALS

Because of easy modification and low immunogenicity, PBA is used as a targeting group to target cancer cells and tumors. In order to achieve the targeting function of PBA, PBA needs to be modified on some functional materials. PBA can participate in organic reactions to get PBA-modified organic small molecules and organic semiconductor polymers. What's more, there are usually two ways to obtain PBA-modified nanomaterials. One way is that the nanomaterials are formed first, and PBA is attached to the materials by chemical bonds (Figure 1A). The other way is to form the structural unit modified by PBA first and then self-assemble it into PBA-modified nanomaterials (Figure 1B).

PBA is used as a chemical recognition group and can conjugate to nanomaterials. Carboxylated and aminoated PBA are bound to nanomaterials by forming amide bonds. The functionalized nanomaterials present the targeting ability for

cancer diagnosis and therapy. For example, hyperbranched amino-functionalized magnetic materials were obtained by decorating hyperbranched polyethylenimine onto Fe_3O_4 nanoparticles,³ and 4-formate phenylboronic acid was chemically modified to the magnetic materials to get a PBA-functionalized drug loading system, which achieved the controlled release of the drug and tumor targeting in the pH-tumor-specific microenvironment. Recent studies have also reported self-assembled functional materials of PBA for targeting tumors. The hydrophilic PEG was generally chosen to react with PBA, and PBA-based functional materials were obtained by self-assembly. For instance, camptothecin–disulfide bond–PEG2000–4-carboxybenzoic acid was self-assembled to form nanomicelles as an active targeting and redox-sensitive pro-drug,⁴ and the nanomicelles achieved disulfide-bond-triggered drug release in the tumor microenvironment with high glutathione concentration. Similarly, Zhang *et al.* developed a multifunctional star micelle system by simply mixing photo-initiated cross-linked amphiphilic copolymers with ligand-bound redox-sensitive amphiphilic copolymers.⁵ PBA-functionalized redox-sensitive amphiphilic copolymers (PBA–PEG–ss-PCL) were formed by PBA, PEG as hydrophilic, and polycaprolactone (PCL) as hydrophobic. Mixed with photo-initiated cross-linked amphiphilic copolymers (six-arm polyethylene glycol-poly(cinnamate-modified ϵ -caprolactone)), the mixture was self-assembled in aqueous solution to form PBA-ss-NCLM micelles, which served as drug carriers to achieve precise controlled release of the drug. Through the above methods, PBA-based functional chemical materials can be designed and synthesized for the cell and *in vivo* imaging and tumor treatment.

3. TARGETING STRATEGIES

PBA can covalently bond with diols to form borate, especially with glucose, fructose, and so on. As one of the main components of the cell membrane, glycoproteins affect the signal transmission of tumor cells. Glycoproteins on the cell surface are closely related to the occurrence and development of tumors, and the excessive expression of glycoproteins directly affects the malignant metastasis of the tumors. These findings show the membrane difference between normal cells and cancerous cells. Based on the reaction of PBA and saccharides, PBA-based nanomaterials as drug carriers were designed to realize the accurate delivery for cancerous cells. The above studies further proved that PBA could still interact with the glycoprotein on the surface of cancerous cells in physiological conditions. The alteration of glycoproteins on the cancer cell surface is mainly manifested by the increase of sialic acid glycopeptide and the change of glycosyltransferase activity. SA is overexpressed on cancer cells such as liver cancer cells, pancreatic cancer cells, and breast cancer cells. Therefore, as a widely used target receptor, SA is used for cancer diagnosis and treatment. PBA has high selectivity and binding affinity to SA and can form reversible boronic acid esters. Otsuka *et al.* studied the equilibrium constant (K) of 3-(propionamido) phenylboronic acid (PAPBA) and SA.⁶ At physiological pH, the equilibrium constant of PAPBA and SA was 7 times higher than that of glucose. The high equilibrium constant indicated that boric acid could selectively recognize SA residues. The high complexing ability of SA and PAPBA was also verified on the borate affinity chromatography at pH 6.5, which showed that PAPBA could combine with SA in the acidic environment of the tumor (pH = 6.5). Therefore,

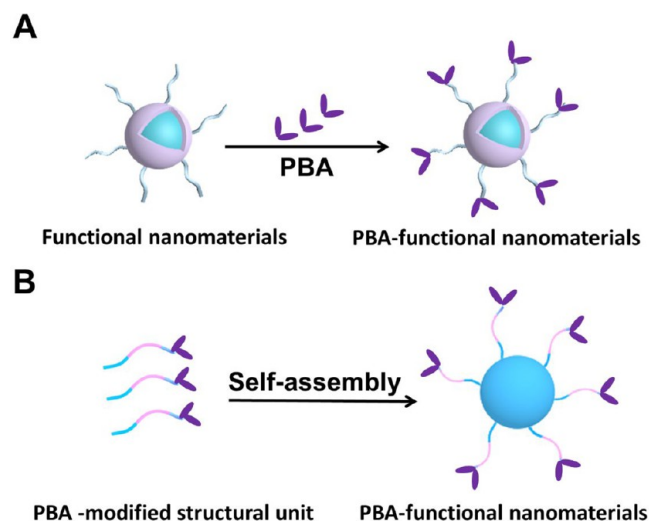


Figure 1. Modifications of PBA on functional materials. (A) PBA is combined to the functional chemical nanomaterials by a chemical bond. (B) PBA-modified structural units are self-assembled as PBA-based functional chemical nanomaterials.

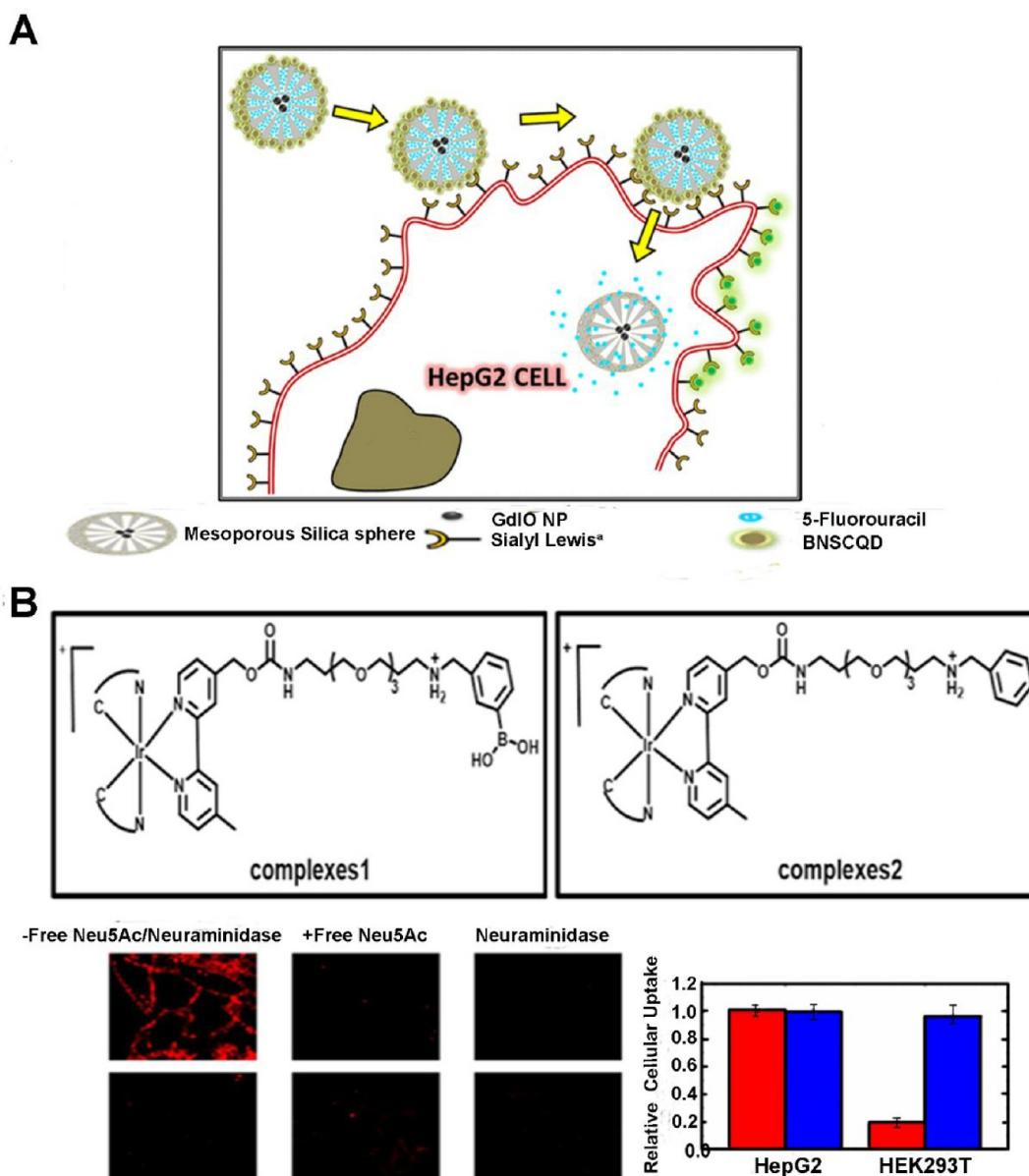


Figure 2. Fluorescence imaging of PBA-based functional materials. (A) Specific targeting schematic of GdIO core@mSiO₂@BNSCQD nanoparticles. Reproduced with permission from ref 8. Copyright 2018 American Chemical Society. (B) Cancer cell specific imaging and uptake of iridium(III) complexes. Reproduced with permission from ref 11. Copyright 2017 John Wiley and Sons.

functional materials modified with PBA have the potential to target SA on the cell surface. Moreover, researchers confirmed the combination of PBA and SA again at a theoretical level through molecular dynamics simulation and density functional theory calculation.⁷ In the case of strong interaction energy, biantennary PBA can spontaneously move to SA, and their binding energy is -181.2479 kcal/mol, indicating the rapid interaction between PBA and SA. These studies indicated that PBA had the potential to form reversible borate with SA residues on the surface of cancer cells. The combination of PBA and SA promotes the uptake of PBA-based functional chemical materials by cells and helps materials accumulate at the tumor site. PBA-based functional chemical materials are expected to be applied in tumor imaging and therapy.

4. FLUORESCENCE IMAGING

Biological imaging is an important technology to study the structure and biological function of cells and organisms. At present, FLI has a wide range of applications in biological imaging because of its high sensitivity, high selectivity, diversity, and noninvasive properties. Usually, FLI is performed by exciting the fluorescent probes through light to generate fluorescence signals for biological imaging, and FLI can be used in cell imaging and *in vivo* imaging. The functionalized fluorescent probes can distinguish effectively between normal cells and tumor cells, as well as normal and tumor tissues, achieving early diagnosis of cancer and imaging-mediated tumor therapy. Fluorescent probes containing PBA groups can recognize an overexpressed glycoprotein, which can realize the fluorescent imaging in cancer cells and tumors. Recently, carbon quantum dots have been developed for applications in

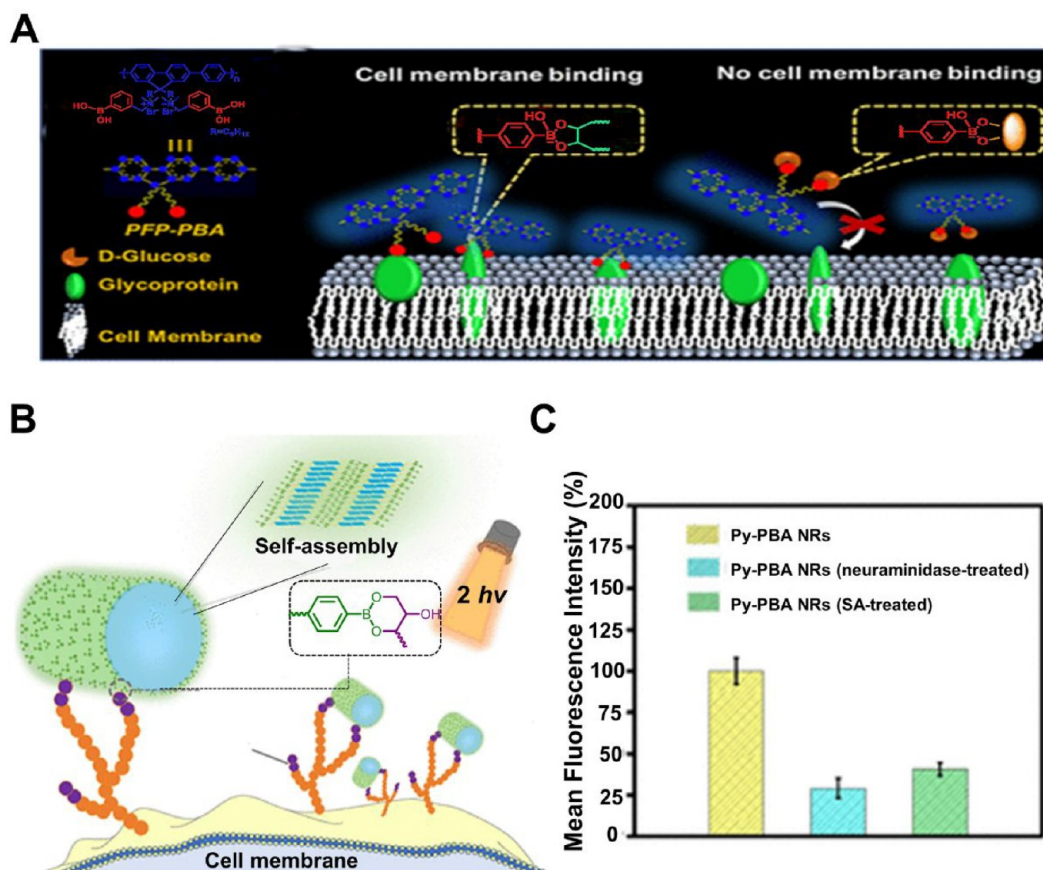


Figure 3. (A) Controllable cell membrane imaging of PFP–PBA. Reproduced with permission from ref 12. Copyright 2019 American Chemical Society. (B) Py-PBA NRs for two-photon imaging of SA. (C) Mean fluorescence intensity of HepG2 cells in the different samples. Reproduced with permission from ref 13. Copyright 2021 American Chemical Society.

biosensing and bioimaging due to their outstanding luminescence properties, photostability, biocompatibility, and water solubility. Researchers designed and synthesized gadolinium oxide-iron oxide (GdIO) core@mSiO₂@BNSCQD nanoparticles, in which a mesoporous silica shell was gated with boronic-acid-functionalized highly luminescent carbon quantum dots (BNSCQDs)⁸ (Figure 2A). BNSCQDs formed drug delivery and MR imaging systems for pH response and cell surface receptor reactions. When nanoparticles reached the tumor environment, the BNSCQDs were isolated and attached to the sialyl Lewis X (SLX) receptors on the surface of cancer cells to bind boric acid groups and SLX, which further increased the fluorescence signal. The fluorescence signal in HepG2 cells was gradually enhanced, which indicated that the particle selectively targeted HepG2 cells. The binding of PBA promoted drug delivery as well as cell imaging. Besides nanomaterials, organic molecular dyes can also bind to PBA. In 2001, Tang *et al.* proposed the concept of aggregation-induced emission (AIE).⁹ AIEgens have no emission or weak emission in the dissolved state. When AIEgens are in aqueous solution, molecular rotation of AIEgens is limited to aggregate emission. AIEgens are beneficial for bioimaging because of their high emission brightness, high light bleaching threshold, and large Stokes shift. Peng *et al.* used tetraphenylethene (TPE) as a fluorophore to link polypeptide and PBA to synthesize the fluorescent probe with the ability of cancer cell membrane targeting.¹⁰ Through the specific binding of PBA to the cell

surface, the probe showed high fluorescence in the aggregation state, demonstrating the ability to target cancer cells. In order to enhance the cell membrane targeting ability, a positive charge structure was connected with PBA. The electrostatic repulsion of the probe was helpful to bind the molecules to carboxylate groups of SA, which increased the ability of the probe to bind to the cell membrane. Transition metal complexes were used as fluorophores to design cyclic metal iridium(III) polypyridine complexes functionalized with APBA, which formed novel luminescent probes and SA imaging reagents (Figure 2B).¹¹ Cell imaging revealed that the probe containing PBA (complexes1) was able to image in HepG2 cells, while the probe without PBA (complexes2) showed weak fluorescence in cells. In the presence of free Neu5Ac and neuraminidase, the probe could not achieve cell imaging due to the reduced binding ability of PBA to SA on the cell surface. Moreover, cancer cells HepG2 and normal cells HEK293T have obviously different levels of SA on the cell surface. Incubated with complexes1 under the same conditions, HEK293T cells showed negligible cell emission, and ICP-MS measurements indicated that the uptake of complexes1 by HEK293T cells was about 5.2 times lower than that of HepG2 cells. These findings suggested that complexes1 was able to recognize SA residues on the cell surface and exhibited cellular discrimination, which provided a new direction for the design of cancer diagnostic probes.

Zhao *et al.* designed molecules based on structures of positive charge and PBA.¹² Cell membrane imaging was also

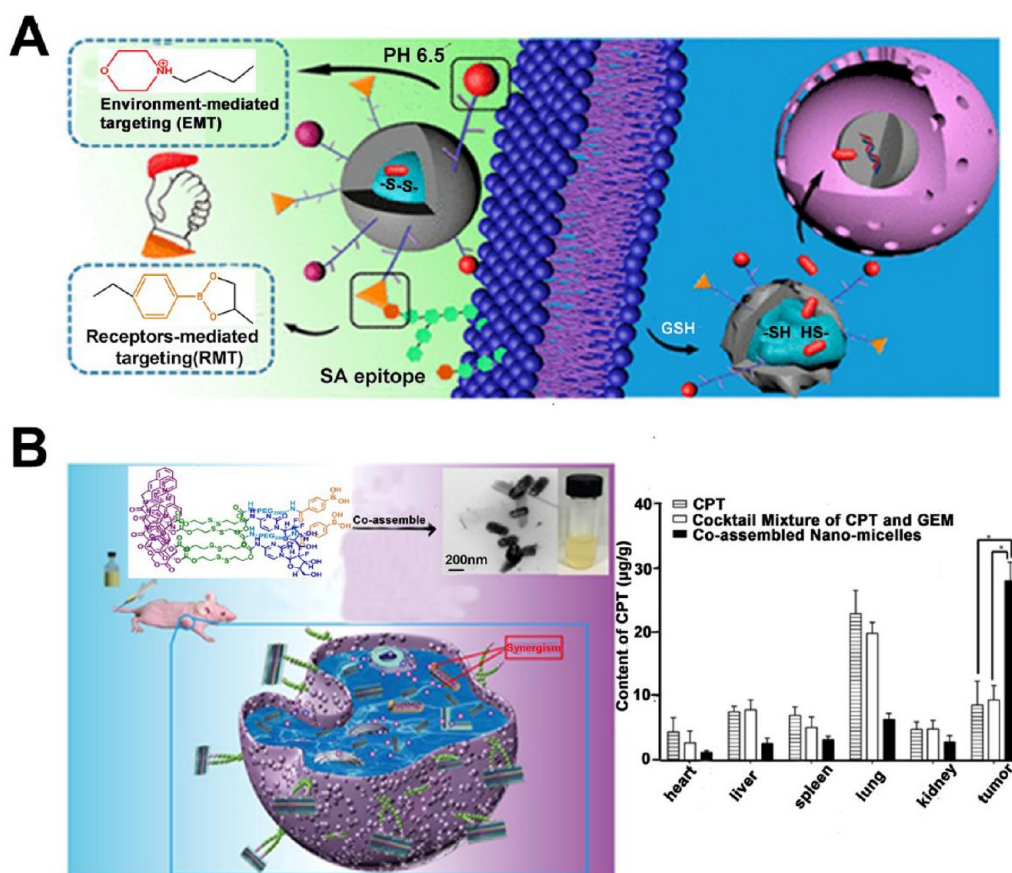


Figure 4. Chemotherapy of PBA-based functional chemical materials. (A) Targeting mechanism of PMNG. Reproduced with permission from ref 16. Copyright 2017 American Chemical Society. (B) Active targeting and redox-controlled synergistic codelivery of CPBA-modified coassembled nanomicelles. Reproduced with permission from ref 4. Copyright 2019 Elsevier.

achieved using tunable electrostatic interactions between negatively charged cell membranes and positively charged functional materials as well as BA-based controllable-assembly systems (Figure 3A). Moreover, cationic conjugated polymers (CCPs) have a π -conjugated structure and strong light-harvesting capability. The PBA-functionalized cationic conjugated polymer (PFP-PBA) could achieve controllable imaging by the dynamic covalent bond between the diol structure of the membrane glycoprotein and PBA as well as the electrostatic interaction. The addition of D-glucose could block PFP-PBA binding sites, reduce their interaction with cells, and inhibit the cell membrane imaging ability of PFP-PBA. Molecular self-assembly is a technology in which molecules use noncovalent bond forces to spontaneously form stable and regular structures. The above contents demonstrated the imaging ability of PBA-functionalized polymers to glycoprotein-overexpressing cancer cells and developed a controllable imaging system for biological applications. To improve the selectivity of PBA-functionalized small molecules, Li *et al.* designed and synthesized PBA-functionalized pyrene derivatives (Py-PBA) and formed nanorods through self-assembly (Py-PBA NRs).¹³ (Figure 3B) Py-PBA NRs could bind specifically to SA, which could help Py-PBA NRs locate and image on the cell membrane. In addition, near-infrared light was used as the excitation light source to achieve two-photon imaging and treatment, which solved the problem of low tissue penetration depth caused by the short absorption wavelength of Py-PBA NRs. In order to evaluate the recognition and imaging ability of Py-PBA NRs for the sialic acid glycans of the

cell membrane surface, Py-PBA NRs and HepG2 cells were incubated together. Bright fluorescence was observed on the cell membrane. After HepG2 cells were pretreated with glycosidase and free SA and incubated with Py-PBA NRs, the fluorescence intensity decreased by 70% and 60%, respectively (Figure 3C). These data supported that the fluorescence on the cell membrane came from the specific binding of SA and Py-PBA NRs. Therefore, this probe could be used as an important tool for imaging the surface of sialylated cells. Although the PBA-based functional materials could distinguish between normal cells and cancer cells, these applications mainly focus on cell imaging, which was not conducive to the realization of clinical applications. Recent studies involved *in vivo* imaging. Researchers designed PBA-functionalized peptide nanotubes (PPNTs), which achieved precise targeting of tumors, deep penetration of tumors, and efficient treatment of metastatic tumors.¹⁴ PPNTs were constructed by integrating anticancer drugs 7-ethyl-10-hydroxy camptothecin (SN38) and indocyanine green (ICG). Based on the dual functions of PPNTs, FLI and reactive oxygen species (ROS) under near-infrared (NIR) laser irradiation achieved tumor imaging and treatment. PPNTs with ICG (I-PPNT) accumulated more in tumor sites than I-PNT and confirmed that PBA-SA interactions promoted tumor targeting, which revealed potential applications in the following treatments. All of the above applications illustrated the potential of PBA-based functional materials for imaging and diagnosis. However, these fluorescent probes had short emission wavelengths, which was not conducive to tissue imaging. With the development of NIR

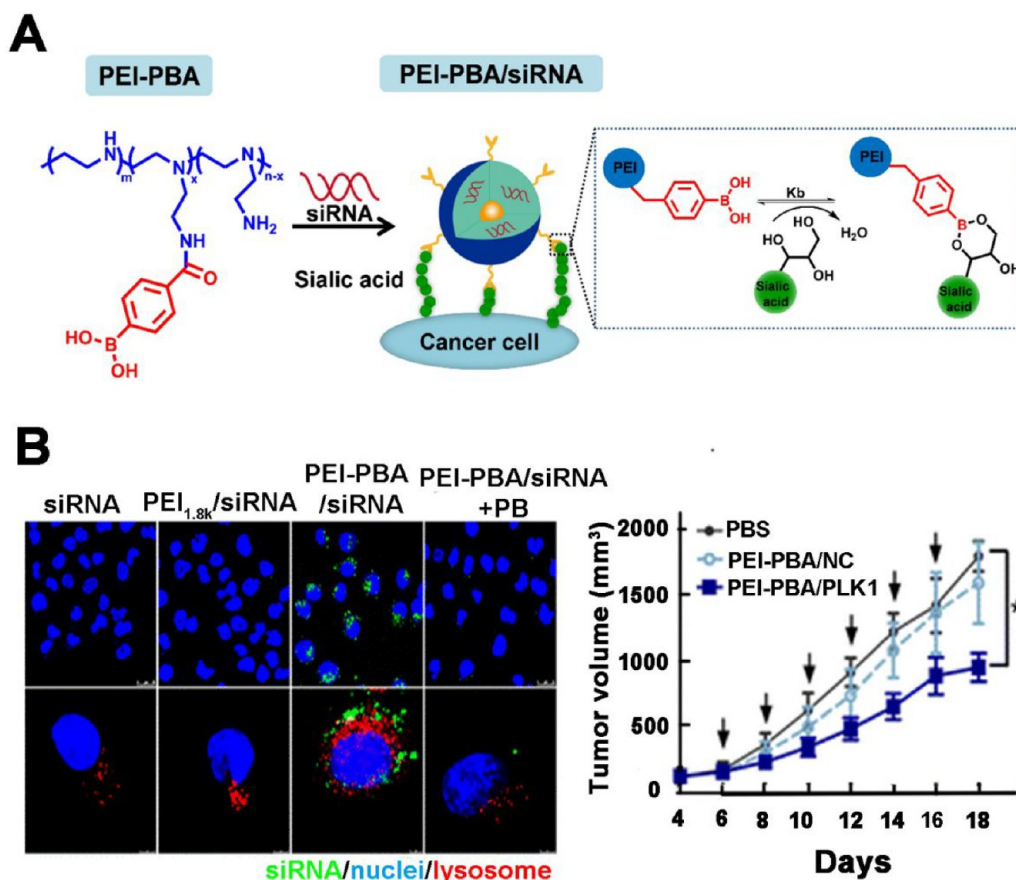


Figure 5. Gene therapy of PBA-based functional chemical materials. (A) Synthesis and delivery of PEI–PBA conjugates. (B) Confocal imaging and anticancer effects. Reproduced with permission from ref 17. Copyright 2017 American Chemical Society.

FLI technology, fluorophores in the second near-infrared wavelength range (NIR-II, 1000–1700 nm) are being exploited. NIR-II FLI has longer excitation and emission wavelengths, which can reduce the scattering phenomenon of light through biological tissues and enhance tissue penetration ability, while PBA-functionalized NIR-II functional chemical materials have not been reported. It is necessary to expand the applications in the biological field by developing NIR-II PBA-based functional materials.

5. TUMOR THERAPY

At present, there are two main ligand presentation strategies for PBA ligands for tumor therapy. One is the direct presentation of PBA on functional materials, which is the most widely used. It is simple and fast but makes it easy to cause nontarget effects. To address this issue, the PBA re-exposure strategy is proposed. First, PBA is protected by the reaction of PBA and diol compounds to form a dynamic phenylboronate ester bond. Then the borate ester bond is broken in the acidic tumor microenvironment, so PBA is re-exposed to achieve targeted tumor therapy.

5.1. Direct Presentation of PBA for Tumor Therapy.

5.1.1. Chemotherapy. Chemotherapy is a kind of pharmacotherapy, which uses anticancer drugs to prevent the proliferation, infiltration, and metastasis of cancer cells and to achieve tumor therapy by killing cancer cells, because chemical drugs are easily cleared by the rapid reticular endothelial system (RES) during blood circulation and cannot gather at the tumor site with a high concentration.

Furthermore, chemotherapeutic drugs cannot distinguish between normal cells and tumor cells, and the inevitable uptake of chemotherapeutic drugs by normal cells will cause systemic toxicity and lead to serious side effects. To improve the therapeutic effect, patients have to repeat administration and long-term use of chemotherapeutic drugs. Therefore, chemotherapy may produce multidrug resistance and bring some side effects. To solve the above problems, nanoparticle delivery systems such as silica and polymers are usually used as drug carriers and combine with targeted ligands to achieve tumor recognition and therapy. The typical anticancer drug doxorubicin (DOX) induces tumor cell apoptosis by inhibiting the activity and disrupting the DNA of topoisomerase II. Huang *et al.* reported a method for preparing multiple double-responsive hollow mesoporous silica nanoparticle (HMSN) drug delivery systems.¹⁵ When the HMSN system loaded DOX reached the tumor site by PBA targeting, the overexpressed glutathione (GSH) and acid environment in the tumor microenvironment disrupted intermediate links and could lead to rapid drug release for tumor inhibition. The obvious tumor inhibition can be observed from tumor volume and weight through *in vivo* experiments. To further improve the targeting ability of DOX, PBA and morpholine (MP) double-modified polypeptide nanogels were constructed for dual targeting¹⁶ (Figure 4A). The nanogels were core cross-linked by disulfide bonds. Intracellular GSH could break down the disulfide bonds to selectively release DOX. The results demonstrated that the combination of receptor-mediated targeting and environment-mediated targeting enhanced

synergistic targeting. Zhang *et al.* developed enzyme and redox dual-reaction polymeric micelles with active targeting ability.⁵ This kind of micelle showed rapid and accurate release of intracellular drugs during cancer therapy. Camptothecin (CPT) is an inhibitor of DNA topoisomerase I. CPT-polymerized prodrugs were formed by conjugating to monomethyl poly(ethylene glycol) (mPEG) via a redox-responsive linker. The enzyme reaction system was obtained by connecting the hydrophilic PCL segment and the hydrophobic segment with an azo bond, and PBA was grafted to the end of the PEG segment. The nanocarrier had active targeting ability. Through receptor-mediated endocytosis, micelles could selectively enter tumor cells, and therapeutic agents could be rapidly released through dual triggers of the enzyme and redox reactions in the cytoplasm, which ultimately had high inhibitory effects on tumor cells and low side effects on normal tissues. To enhance tumor therapeutic efficacy, multiple drug synergistic therapeutic strategies were used. Xu *et al.* reported a 4-carboxyphenylboronic acid (CPBA)-decorated rod-shaped nanomicelle, which realized the synergistic combination self-delivery of CPT and gemcitabine (GEM) (Figure 4B).⁴ CPBA-modified coassembled nanomicelles have significantly enhanced cellular internalization, while the cellular uptake of free CPBA pretreated cells was significantly reduced. The results proved the active targeting ability of the PBA-mediated synergistic assembly of nanomicelles. *In vivo* biodistribution analysis suggested that coassembled nanomicelles preferentially aggregated at the tumor site, which reduced side effects and improved the therapeutic ability of the drugs.

5.1.2. Gene Therapy. Previous studies have shown that the occurrence and development of malignant tumors are closely related to gene expression or dysregulation, so gene therapy has become a treatment that researchers pay attention to. Gene therapy refers to the introduction of exogenous normal genes into target cells. The introduced genes will correct or compensate the defects and abnormal genes that cause the diseases and achieve cancer treatment. The commonly used genes include siRNA, DNA fragments, mRNA, and miRNA. However, due to their low stability, low bioavailability, and side effects, they are not good for direct clinical application. In recent years, with the development of nanocarriers, nonviral vectors based on cationic nanoparticles, such as liposomes, cationic polymers, and micelles, have been applied to gene delivery due to good safety and transfection efficiency. Ji *et al.* synthesized amphiphilic PBA-functionalized polyethylenimine (PEI-PBA) nanoparticles as an siRNA delivery system and evaluated their antitumor effects¹⁷ (Figure 5). MCF-7 cells were used to evaluate the effect of PBA functionalization on cell binding and siRNA uptake. The fluorescence signal of PEI-PBA/siRNA was significantly higher than free siRNA and PEI1.8k/siRNA, indicating increased uptake. The blocking of SA with 3-aminophenylboric acid significantly inhibited the intracellular siRNA and confirmed the pivotal role of PBA-SA interaction on targeting. Polo-like kinase 1 (PLK1) was selected as a target gene in mouse antitumor experiments. The mice were injected with PBS, PEI-PBA/siPLK1, or PEI-PBA/siNC. PBS or PEI-PBA/siNC did not affect tumor growth, but PEI-PBA/siPLK1 nanocomposites significantly inhibited tumor growth, mainly due to the inhibition of tumor growth by down-regulating the expression of PLK1 genes in tumors.

Amine-terminated polyamidoamines (PAMAMs) are candidates as gene carriers. PAMAMs are a synaptic dendrimer with water solubility, high charge density, and a large number of amine groups. At the same time, their amino-rich structures can promote lysosomal escape and protect nucleic acids from degradation in the acidic pH and enzymatic environment by enhancing "proton sponge" effects. Song *et al.* successfully attached the PBA to the PAMAM surface via a poly(ethylene glycol)- α -maleimide- ω -*N*-hydroxysuccinimide named PPP.¹⁸ PPP was used as a system to achieve intracellular miR-34a delivery. Through the PBA-mediated endocytosis pathway, PPP/miR-34a nanoparticles could significantly induce apoptosis and inhibit cell migration. Moreover, by intravenous injection, PPP-mediated miR-34a delivery was more effective than PAMAM nanoparticles due to enhanced specific targeting ability and prolonged blood circulation time after modifying PBA. Simultaneously, in another study reported by Yang *et al.*, PAMAM modified by PBA (PP) could be used as an effective gene carrier, which would be beneficial to the clinical treatment of cancer in the future.¹⁹ The researchers also used PP as a gene vector for short GC-rich DNA (GCD) delivery. GCD showed good anticancer activity, which could increase the expression of p53 genes in cells and inhibit the proliferation and migration of tumor cells. PP could mediate GCD transfection and had a good tumor targeting ability. Besides, PP/GCD nanoparticles could induce depolymerization of HepG2 cell microtubules, resulting in antiproliferation and antimigration effects. PP/GCD nanoparticles were used for intravenous HepG2 tumor-bearing nude mice and showed better anticancer responses than PAMAM/GCD due to the specific targeting ability of PP. PP/GCD nanoparticles exhibited good biocompatibility in the main organs, and they could cause obvious apoptosis *in situ* in tumor tissues. Dz13, as a DNA enzyme, showed great antitumor effects by reducing the expression of matrix metalloproteinase (MMP)-2 and MMP-9 in tumors. However, the clinical application of Dz13 was seriously hindered due to a low stability and cell uptake efficiency. Yang *et al.* applied PP for gene delivery.²⁰ PP/Dz13 nanoparticles were synthesized, and the transfection function was studied carefully. The inhibition of cell proliferation and migration was investigated, and the data suggested the potential of the gene vector for cancer therapy and promoted future clinical applications of cancer gene therapy. The research of novel gene vectors based on PBA is still on the way. By expanding the regulation of PBA with SA on the cell surface, the transmission of genes in tumor sites can be promoted effectively.

5.1.3. Imaging-Guided Phototherapy. Phototherapy (PT) makes the therapeutic site more accurate and minimizes unnecessary side effects due to the controllability of light. Compared with chemotherapy, PT is noninvasive and a promising strategy for cancer treatment. PT includes photothermal therapy (PTT) and photodynamic therapy (PDT). Moreover, with the development of imaging technology, imaging-guided tumor therapy is a new cancer treatment technology. During the PTT, heat is produced by light irradiation, and the cells at the irradiation site are damaged, which achieves cancer treatments. The frequently used photothermal agents mainly include gold nanoparticles (AuNPs), polydopamine (PDA), and magnetic nanoparticles. Yin *et al.* first proposed plasmonic molecular imprinted nanomaterials for near-infrared targeted PTT of cancer.²¹ Gold nanorods (AuNRs) were used as core plasmonic

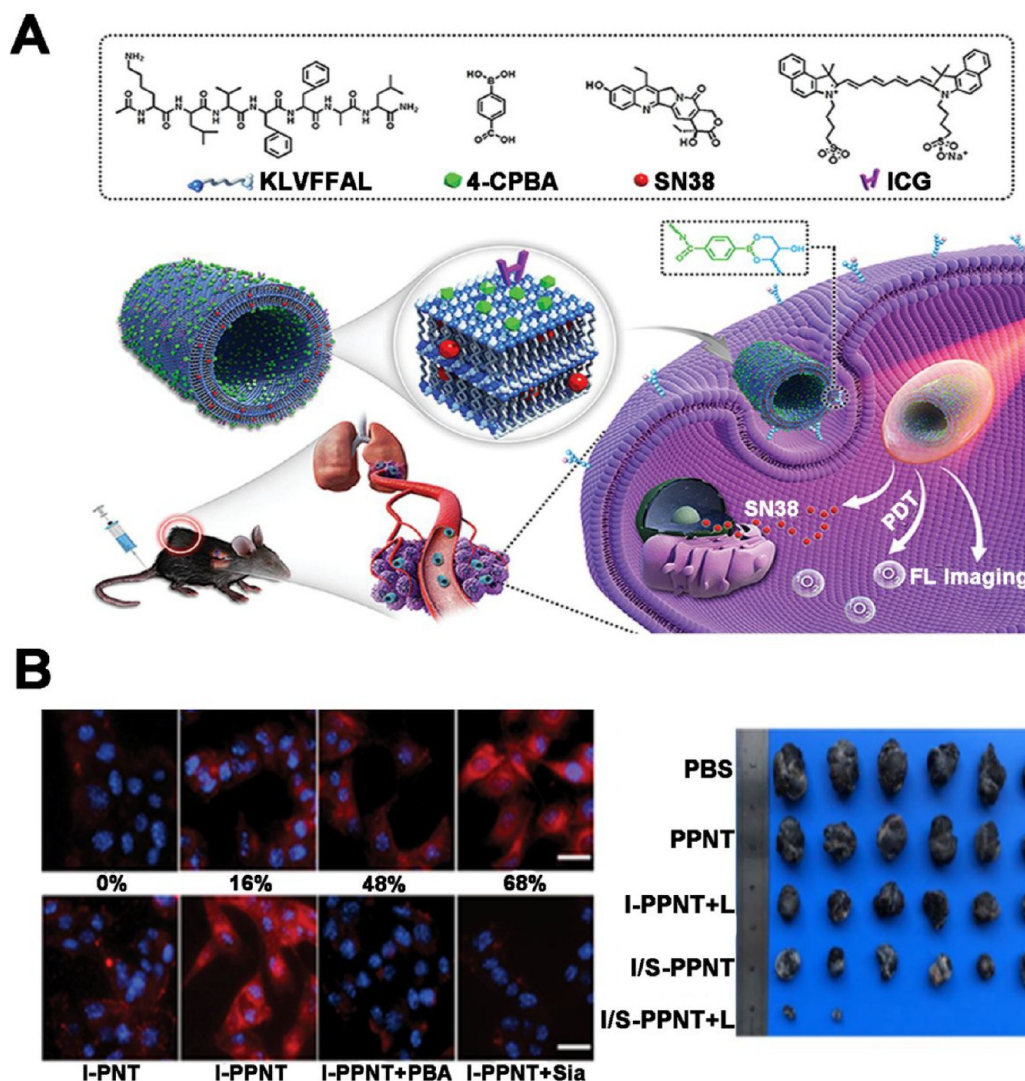


Figure 6. Imaging-mediated phototherapy of PBA-based functional chemical materials. (A) Schematic illustration of the multifunctional nanoplatform. (B) CLSM images of I-PPNTs with different graft density of PBA and CLSM images of different nanotubes. Reproduced with permission from ref 14. Copyright 2019 John Wiley and Sons.

nanomaterials, while SA was used as a template for the preparation of molecular imprinted polymers (MIPs). This kind of MIP achieved fluorescence imaging-guided PTT by doping fluorescent dyes. By intravenously injecting into tumor-bearing mice, bright fluorescence at the tumor site could be observed through *in vivo* distribution. With the aid of SA, the material could selectively accumulate at the tumor site. The PTT was realized under 750 nm laser irradiation. Iron oxide (Fe_3O_4) nanomaterials have been widely used in the construction of thermosensitive platforms. Liu *et al.* coated PDA on the surface of LAPONITE (LAP)- Fe_3O_4 nanomaterials, which enhanced the surface modification ability and PTT effect of the materials.²² Meanwhile, modified PBA photothermal nanomaterials showed selective targeting and multimode imaging. The magnetic resonance (MR) image of the tumor darkened after intravenous injection, while the photoacoustic (PA) signal increased. The nanomaterial could accumulate in the tumor after blood circulation. The MR signal intensity of tumors with the targeted and nontargeted groups decreased by 38.4% and 19.6% at 40 min, and the PA intensity increased from 0.47 to 1.46 and 0.62, respectively.

The targeting of PBA showed a good inhibitory effect on the tumor within 2 weeks. For PDT, the photosensitizer absorbs light to produce reactive oxygen species (ROS), and ROS can produce cytotoxicity. A large amount of ROS accumulates in cells to cause apoptosis. The typical photosensitizers include porphyrin, chlorophen e6 (Ce6), methylene blue, indocyanine green (ICG), etc. Lei *et al.* designed and synthesized PBA-functionalized multivalent peptide nanotubes (PPNTs) to achieve precise tumor targeting, in which the loading of ICG and anticancer drug SN38 enabled I/S-PPNTs to release chemotherapeutic drugs¹⁴ (Figure 6A). To highlight the role of PBA-SA in targeting, confocal imaging was performed using PNTs with different graft densities of PBA (Figure 6B). With the increase of graft density, the intracellular fluorescence intensity increased continuously, but the fluorescence intensity decreased significantly in cells incubated with PBA and Sia, demonstrating the ability of PBA to target cells with overexpressed SA. The solutions of PBS, PPNT, I-PPNT, and I/S-PPNT were injected intravenously at the same ICG and SN38 doses to prove the efficacy of tumor therapy. Approximately 90.0% of tumor inhibition was observed in I/S-

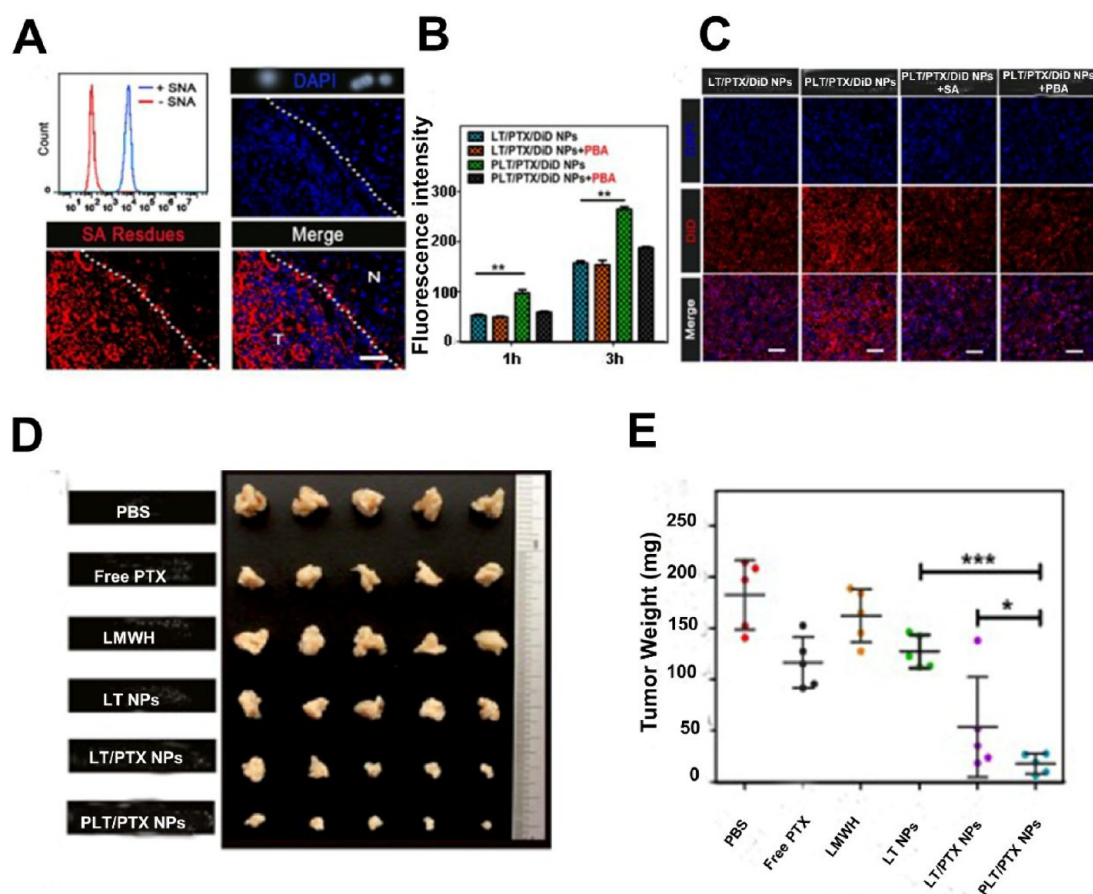


Figure 7. Immunotherapy of PBA-based functional chemical materials. (A) The detection results of SA residues on the surface of PAN02 cells and the immunofluorescence results of PAN02 pancreatic tumor tissue. (B) Statistics of competitive uptake assays analyzed by flow cytometry. (C) CLSM images of PAN02 cells after incubation with LT/PTX/DiD NPs, PLT/PTX/DiD NPs, PLT/PTX/DiD NPs + SA, or PLT/PTX/DiD NPs + PBA for 3 h. (D) Images of pancreatic tumors and (E) the tumor weight of pancreatic tumor-bearing mice treated by PBS, free PTX, free LMWH, LT NPs, LT/PTX NPs, or PLT/PTX NPs. Reproduced with permission from ref 26. Copyright 2021 Elsevier.

PPNT-mediated combination PDT and chemotherapy therapy. The combination of precise targeted and locally activated treatment enabled high accumulation of PPNT materials in tumors and exhibited significant tumor growth inhibition and pulmonary metastasis inhibition. I/S-PPNT was expected to be an intelligent nanoplatform for accurate and efficient imaging-guided therapy of metastatic tumors. Besides commercial photosensitizers, another optical material upconversion nanomaterial (UCNP) excited by near-infrared light to produce ROS has attracted researchers. UCNPs are optical nanomaterials doped with lanthanide ions, which can produce UV–vis emission through NIR light excitation. Wang *et al.* designed a dual-target nanoplatform guided by dual-color fluorescence imaging.²³ The nanoplatform was constructed by aminophenylboronic acid (APBA)-functionalized UCNP (APBA-UCNPs) and hyaluronated fullerene (HAC60) via specific binary borate condensation. The fluorescence resonance energy transfer (FRET) between APBA-UCNPs and HAC60 facilitated the generation of $^1\text{O}_2$. The nanomaterial could simultaneously target polysialic acid and CD44 to achieve accurate targeting of tumor cells. By cell experiments, the targeting ability of PBA to PC12 cells with highly expressed SA was demonstrated. At the same time, the dual-targeting UCNPs showed stronger fluorescence intensity in tumor cells, which indicated that dual targeting promoted tumor cell uptake. Although the study was only at the cell level, it laid the

foundation for further *in vivo* treatment. At present, the functional materials based on PBA used in phototherapy as photosensitizers and photothermal agents will be explored as effective drugs to achieve accurate phototherapy.

5.1.4. Immunotherapy. Cancer immunotherapy is a great potential tumor treatment method. The main role of immunotherapy is to guide the body's own immune system to attack tumor cells by targeting tumor antigens, and enhance the existing antitumor immune response to achieve the effect of tumor treatment. Current immunotherapy methods include targeted antibodies, cancer vaccines, immune checkpoint inhibitors, and cytokines. Although the above treatment methods have brought many benefits for tumor treatments, immunotherapy still has disadvantages such as tumor immune escape, low response rate, and systemic toxicity. To improve the clinical application of immunotherapy, researchers have combined nanomaterial delivery systems with immunotherapy to improve tumor treatment effects. Curcumin is an immunomodulator for tumor treatment, which can reduce the expression of programmed death ligand (PD-L1). Curcumin inhibits T-cell immunity through the interaction of programmed cell death protein 1 (PD-1) and PD-L1 to achieve the purpose of tumor treatment. However, curcumin has strong hydrophobicity and low bioavailability, which is not conducive to tumor treatment. To improve the therapeutic effect of curcumin, Jung *et al.* utilized the interaction of

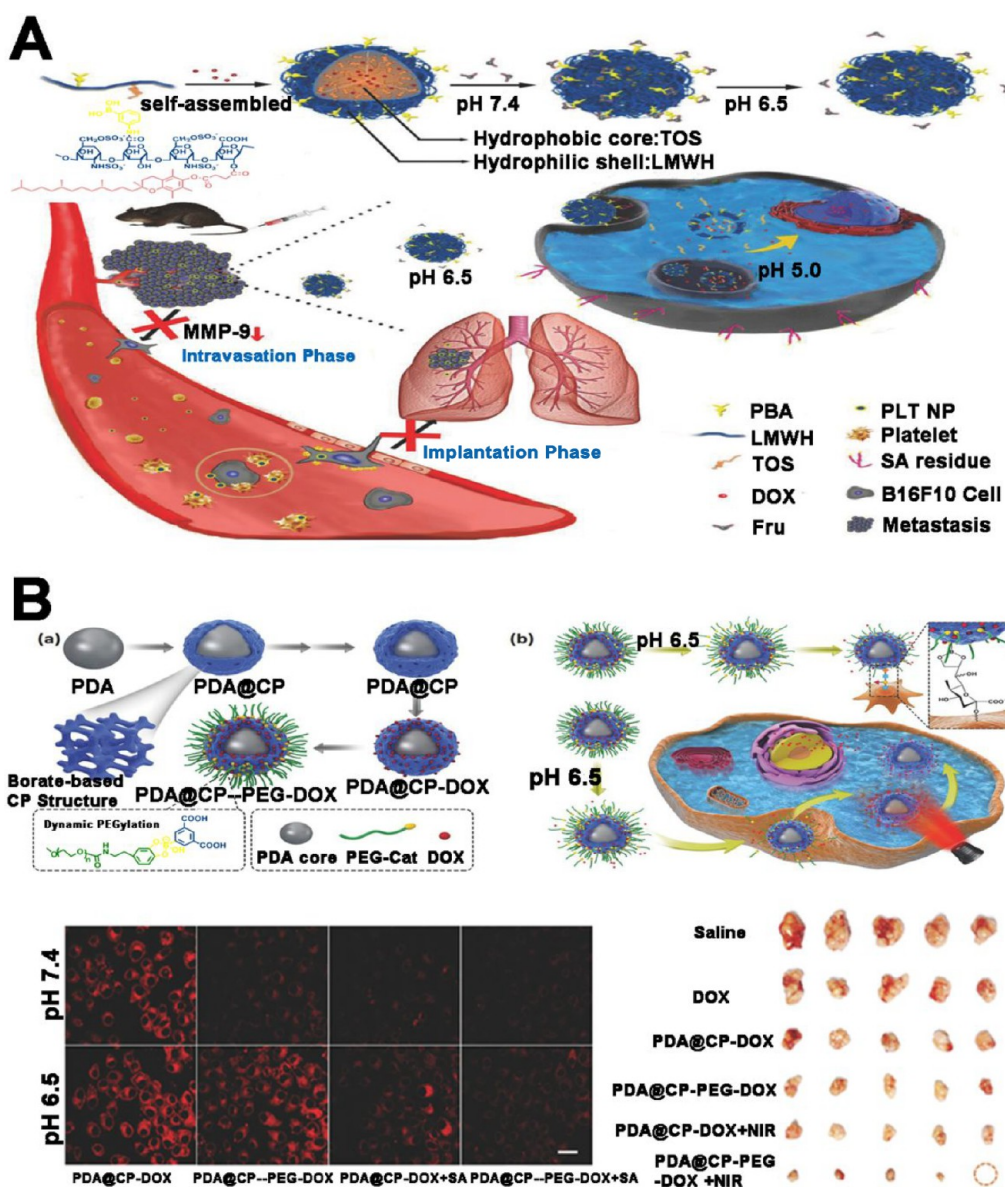


Figure 8. Re-exposure of PBA to tumor therapy. (A) The “Fru-blocking” strategy and the targeting of PLT/DOX NPs. Reproduced with permission from ref 27. Copyright 2018 John Wiley and Sons. (B) The synthesis and targeted therapy of PDA@CP-PEG-Dox. Reproduced with permission from ref 28. Copyright 2018 John Wiley and Sons.

curcumin and PBA to prepare core–shell nanomaterials (pPBA).²⁴ The construction of the nanomaterials solved the hydrophobic problem of curcumin and improved the enrichment ability of curcumin at the tumor site. Similarly, Lim *et al.* mixed pPBA with antibodies to prepare pPBA–antibody nanocomplexes, which mainly used the formation of pH-responsive phenylborates between PBA and the diol on the inherent glycosylation sites of antibodies.²⁵ Compared with free antibodies, pPBA–antibody nanocomplexes achieved pH-responsive release of antibodies and could better accumulate at tumor sites *in vivo*. The above two nanomaterials successfully achieved accumulation at the tumor site and tumor immunotherapy by the enhanced permeability and retention (EPR) effect. However, the EPR effect has tumor heterogeneity, so it needs to improve the specific tumor targeting. As a commonly used targeting receptor, overexpressed sialic acid on the surface of cancer cells could specifically bind to PBA. PBA-based functional materials achieved the specific targeting

of cancer cells overexpressing SA. Lu *et al.* synthesized 3-aminophenylboronic acid modified with low molecular weight heparin-*D*- α -tocopherol succinate micellar nanoparticles (PBA-LMWH-TOS NP, PLT NPs).²⁶ LMWH could competitively bind with P-selectin and interfered with the binding of a P-selectin/P-selectin glycoprotein ligand-1 (PSGL-1) to inhibit the adhesion between vascular endothelial cells (VECs) and myeloid-derived suppressor cells (MDSCs). The infiltration of effector T cells and the efficacy of antipancreatic tumors were enhanced. PBA could bind to SA on the surface of cancer cells to promote the uptake of PLT NPs. In Figure 7A, it was first demonstrated that PAN02 cells and PAN02 orthotopic pancreatic tumor tissues overexpressed SA. The targeting ability of the PLT NP was evaluated *in vitro* in Figure 7B. 1,1-Dioctadecyl-3,3,3,3-tetramethylindodicarbocyanine fluorescein (DiD) was loaded on the nanomaterials as a probe PLT DiD/PTX NP. The fluorescence intensity of PAN02 cells treated with PLT DiD/PTX NPs were significantly stronger than cells

treated with LT/PTX NPs. The results of confocal imaging also showed that PLT DiD/PTX NPs could combine with SA on the surface of PAN02, which enhanced the uptake of nanomaterials by the cells (Figure 7C). To prove the targeting ability of PBA *in vivo*, the inhibitory effect of PLT/PTX NPs on tumor-bearing mice was studied. As shown in Figure 7D,E, PBA modification endowed PLT/PTX NPs higher antitumor efficiency. The construction of PLT/PTX NPs provided a new strategy for the treatment of pancreatic cancer.

5.2. Re-Exposure of PBA to Tumor Therapy. Although PBA-based functional materials have been used to achieve accurate tumor targeting and therapy, the simple combination of PBA-SA is inevitable in some tissues. Especially liver and lung tissues also express SA residues to some extent, which can lead to nontarget effects. Recent studies illustrated that the phenylboronate dynamic bonds could achieve PBA re-exposure in the tumor microenvironment, which reduced the off-target effects of nanomaterials, thus reducing the uptake of materials by normal cells. Long *et al.* constructed a simple self-delivering micellar NP consisting of antitransfer complex low molecular weight heparin (LMWH) and D- α -tocopheryl succinate (TOS), but the micelle did not possess targeting properties.²⁷ To optimize the micelle, APBA was combined with NPs to form PBA-LMWH-TOS nanoparticles (PLT NPs) (Figure 8A). At the same time, to reduce the off-target effect, the researchers proposed a "Fru-blocking" strategy to combine PBA with monosaccharide. At physiological pH, phenylboronic acid ester remained stable. In the tumor microenvironment, PBA was re-exposed to target SA on the cancer cell surface. Encapsulation of DOX in PLT NPs enhanced the treatment of melanoma as well as metastasis inhibition. The researchers compared the cell accumulation efficiency of cancer cells with overexpressed SA residues and COS-7 cells with low expressed SA residues. The uptake of PLT/DOX NPs by cancer cells was significantly higher than that of COS-7 cells. The result was further validated by competitive inhibition assays. Free PBA and SA could reduce PLT/DOX NP internalization but had no effect on LT/DOX NPs, which suggested that PBA could target SA in an acidic tumor microenvironment. Antitumor experiments *in vivo* also showed that PLT/DOX NPs had a more obvious effect on tumor treatment. Therefore, the simple targeting strategy based on tumor-microenvironment activation of PBA is promising for the treatment of tumors overexpressing SA residues. Similarly, based on the strategy, Liu *et al.* designed a novel cancer treatment nanoplatforM for chemo-photothermal synergistic therapy by dynamic PEGylation of borate-based coordination-coated PDA nanoparticles (PDA@CP-PEG) (Figure 8B).²⁸ PBA-functionalized coordination polymer (CP) layers could be assembled on PDA nanoparticles. The PEG molecules of catechol capping were immobilized on the CP layer functionalized with PBA to synthesize PDA@CP-PEG nanocarriers. The experimental results indicated that the PDA@CP-Dox group showed considerable fluorescence signals at pH 7.4, while the cells incubated with PDA@CP-PEG-Dox showed significant weak fluorescence. However, the fluorescence signal of the PDA@CP-PEG-Dox group increased significantly when the pH value decreased to 6.5. The pH induced the cleavage between PBA and the catechol group and enhanced the ability of PBA to target SA. The excellent antitumor effect of nanoparticles *in vivo* was verified by monitoring the change of tumor size. Selective exposure of PBA in the tumor microenvironment improves cancer cell uptake and tumor therapeutic efficacy.

6. CONCLUSION AND PERSPECIVES

In this mini-review, we summed up the fluorescence imaging and tumor treatment based on PBA targeting. Both fluorescence imaging and tumor therapy have demonstrated the efficient targeting ability of PBA to cancer cells and tumors, and tumor-targeted therapy can be achieved through direct targeting and re-exposure of PBA, including chemotherapy, gene therapy, and phototherapy. PBA can bind to biological molecules such as sugars and nucleotides in organisms, which is not conducive to PBA-based functional materials to achieve tumor-specific targeting. The development of tumor microenvironment responsive PBA-based functional materials may be able to solve the above problem, avoiding the targeting group PBA from binding to biomolecules before reaching the tumor site. At present, most of the PBA-based functional materials used for cancer treatment are nanomaterials. Small-molecule drugs have good reproducibility, easy metabolism, and low toxicity, so the development of small-molecule compounds based on PBA ligands can become a direction for anticancer drugs. In addition, phototherapy, as a controllable and accurate treatment, combined with biological imaging, the development of imaging-guided photothermal agents, and photosensitizers, can compensate for the vacancy of PBA ligand-targeted tumor therapy. PBA-based functional materials have become a kind of promising biomedical materials.

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Notes

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