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REVIEW

iRADIOLOGY

A review of biomodified or biomimetic polymer dots for targeted fluorescent imaging and disease treatments

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Abstract

Due to their inherent tunable spectrum, high brightness, excellent biostability and biocompatibility, and functionalization of surfaces, semiconducting polymer dots (Pdots) are now playing an essential role in fluorescent (FL) imaging and disease treatment through bioconjugation with peptides or biomimetic materials. In particular, biomimetic Pdots exhibit their capability in targeted imaging of lesion and increased efficacy for targeting disease treatment. This review will inspect the recent advances in the design and functionalization strategies of biomodified and biomimetic Pdots for enhanced disease detection and therapy. More importantly, the application of these two modifications in targeted FL imaging and cancer treatment is to be addressed in detail. Meanwhile, the main challenges and prospects of biomimetic and biomodified Pdots are to be discussed, which will pave a new avenue for improved disease detection and imaging-guided treatment.

KEYWORDS
biomimetic, biomodified, cancer treatment, fluorescent imaging, semiconducting polymer dots

1 | INTRODUCTION

To date, multifunctional nanoplatforms have been constructed to serve as biosensors, imaging diagnostic probes, drug delivery systems, and theranostics agents for various diseases [1–10]. In addition, fluorescent (FL) imaging exhibits high sensitivity in mapping the whole-body biodistribution of drugs or visualizing real-time biological processes in a living organism [11–14]. Interestingly, inorganic metal- or nonmetal-based and organic

Abbreviations: AF, activated fibroblast; BBB, blood–brain barrier; CM, cancer cell membrane; Dex-Pdots, dextran-functionalized Pdots; NIR, near-infrared; NK, natural killer; NK-NPs, NK cell-membrane-decorated nanoparticles; PA, photoacoustic; PAI, PA imaging; TAC, tetrameric antibody complex.

molecular-based nanoparticles have been developed and used as contrast agents for FL imaging for cells and drug release tracking and therapeutic agents for the treatment of cancer or brain disorders [15–19].

More importantly, due to the tunable optical properties, high quantum yield, abundant functional groups, exceptional photostability, and excellent biocompatibility, FL semiconducting polymer dots (Pdots) are attracting extensive attention as promising theranostic agents [11]. In particular, bright FL Pdots have been produced by using a variety of techniques, demonstrating their advantages in in vitro and in vivo imaging through simple functionalization with antibodies or other biomolecules [12]. Besides, biomimetic Pdots can also be used as contrast agents for high-sensitivity detection of in vivo subcutaneous and brain tumors in the second near-infrared (NIR) II window [16–19].

In addition, the integration of multifunctional diagnosis and treatment components into a single nanoplatform is essential for the early detection of disease, therapeutic agent targeting evaluation, and real-time monitoring of therapy response, offering the ability for individualized precision medicine [13, 14, 20]. However, conventional nanoprobes or nanoparticle-based drug delivery systems frequently experience challenges, such as early immune system recognition, quick reticuloendothelial system (RES) clearance, and poor accumulation at tumor sites, which might hamper their potential clinical applications [21]. Therefore, it is extremely important to develop surface-modifying nanoprobes with synthetic polymers or specific ligands for targeted and enhanced disease theranostics [21–23].

Meanwhile, cell membrane-coated nanoparticles have been inspected for various biomedical applications, such as cancer theranostics [24–26], detoxification [27], vaccination [28], and drug delivery [29]. In particular, biomaterials, such as cell membrane or the outer membrane of bacteria, can be coated on the surface of nanoparticles to offer the new nanoplatform native biological capabilities [30]. For example, the full set of cell membrane components from various categories of cells can be extracted and coated onto the surface of nanoparticles, producing the biomimetic nanoplatform that can maintain the cellular property and adaptability [31–33]. Interestingly, nanoparticles with an active red blood cell membrane exhibited prolonged circulation time and reduced accelerated blood clearance [34, 35]. In addition, biomimetic nanoparticles also showed the ability to pass blood–brain barrier (BBB) and target glioma tumor for enhanced treatment [36, 37].

More specifically, Pdots are typically functionalized with amphiphilic polymers, such as the poly(styrene-co-maleic anhydride) and poly(styrene-polyethylene glycol-carboxyl) [12, 38, 39], to formulate surface carboxyl groups. The carboxyl groups in Pdots enable bioconjugation by standard carbodiimide chemistry [40]. By contrast, the biomimetic Pdots are commonly produced by the chemical process of electrostatic adsorption [41].

Therefore, this review summarizes the recent advances in biomodified and biomimetic Pdots for FL imaging and cancer treatment. We demonstrate the biological applications of Pdots in targeted cell imaging [42] and the development of dextran-functionalized Pdots (Dex-Pdots) for dynamic cell tracking [43]. In addition, biomodified Pdots that might escape from the immune system or have been developed into multifunctional agents for bacterial killing are also illustrated [44]. Further, the development of various biomimetic Pdots for tumor detection [45, 46] and high efficacy tumor-specificity cancer treatment is addressed [47]. More specifically, we also present the recent work on how biomimetic Pdots can cross the BBB for enhanced glioma detection [16, 48]. Finally, we also demonstrate how these Pdots functionalization procedures can affect their photophysical properties, further improving their FL molecular imaging capability and enhancing the efficacy of disease treatments. Therefore, these biomodified and biomimetic Pdots will open a new avenue for their potential biomedical applications and clinical translation.

2 | BIOMODIFIED PDOTS FOR TARGETED FLUORESCENCE IMAGING

Although Pdots continue to serve as FL probes in bioanalysis and biomedical imaging [12, 49, 50], Pdots are generally held together by relatively weak and entropically driven hydrophobic interactions. Therefore, like other nanoparticles, they might exhibit low particle stability due to hydrophobic interactions that are moderately strong and driven by entropy [12, 49]. For example, Pdots with anionic surface chemistry are colloidally destabilized at low pH and high ionic strength and are prone to nonspecific binding with proteins [49]. Another limitation of Pdots is the lack of surface modification chemistry and bioconjugate chemistry. Presently, carbodiimide-mediated conjugation in surface carboxyl groups is the most commonly used chemistry. The downside of carbodiimide-mediated conjugation is its poor control and reproducibility in terms of the number and orientation of biomolecules per Pdot [38]. Interestingly, amphiphiles functionalized with poly(ethylene glycol) are becoming the ideal way for the synthesis of Pdots although they are also frequently used for bioconjugation with carbodiimide chemistry. Further, depending on their surface chemistry and surroundings,

Pdots might also show poor colloidal stability and fouling [18, 40, 50, 51]. Therefore, the successful modification of the Pdot surface with coated materials that have robust aqueous solubility, minimal nonspecific interactions with biomolecules, and support well-controlled bioconjugate chemistry is essential for the construction of highly biocompatible and multifunctional nanoprobes for cancer theranostics.

2.1 | Biomodified Pdots for live-cell imaging

Recent studies demonstrated that Pdots might take distinct routes for endocytosis and intracellular trafficking. In particular, Pdots are transported into and destined for lysosomes, implying that bioactive cargos, such as DNA, RNA, and proteins, are unable to maintain intracellular functions [52]. Besides, the amount and rate of Pdots uptake by epithelial cells were significantly decreased. Therefore, to enhance the cellular uptake of Pdots and prevent lysosomal breakdown, increased contacts with the cell surface might be achieved by coating the nanoparticles with cationic lipids or linking the nanoparticles with particularly targeted ligands [41, 50, 51, 53, 54]. Interestingly, cell-penetrating peptides, such as short peptides, are able to promote the cellular update of a variety of probes. For example, Pdots coated with a peptide called cell-penetrating peptide (R8) illustrated that their endocytic uptake efficiency was 15 times higher than that of carboxy Pdots and over 200 times higher than that of pure Pdots only [55]. To examine the R8-mediated cellular uptake and intracellular transport in live HeLa human cervical cancer cells, Zhao et al. linked FL Pdots with a synthetic octaarginine peptide. Besides, PFBT-bound Pdots were conjugated to the R8 peptide via electrostatic interactions on the surface, increasing the biodistribution of nanocarriers (Figure 1) [55–57]. It was discovered (Figure 1b) that R8-Pdots had a positive zeta potential of +29 mV, indicating that R8 was able to successfully alter the zeta potential of normally negatively charged Pdots via electrostatic adsorption. R8-Pdots also showed that they were able to penetrate the cells with a high concentration in minutes, compared to unmodified Pdots, which took several hours to infiltrate the epithelial cells (Figure 1c). In addition to serving as imaging probes and drug transporters, R8-Pdots also elevated the level of autophagy in HeLa cells, demonstrating that they might have the ability to directly control cellular homeostasis (Figure 1d,e) [42]. However, R8-Pdots may not directly enter the double-membraned vesicles for autophagy induction because they are not destined for lysosomal degradation. Importantly, nanoparticle-induced autophagy has been used to treat tumors and neurodegenerative diseases in a synergistic manner. As a result, R8-Pdots as a novel autophagy inducer for the first time open a new avenue for the development of Pdots-based theranostic reagents.

2.2 | Biomodified Pdots for cell labeling

Pdots are a subclass of conjugated polymer (CP) nanoparticles with high (>50%) semiconducting polymer mass or volume concentrations, hydrophobic cores, and small diameters. Pdots have been used for cellular labeling [46], chemical and biochemical sensing [58, 59], and photodynamic therapy [60, 61]. However, to improve their functions in bioanalysis and imaging, the modification of the Pdots surface with a coating material that demonstrates robust aqueous solubility, minimal nonspecific interactions with biomolecules, and well-controlled bioconjugate chemistry is one of the strategies to develop Pdots-based multifunctional nanoplatforms.

More interestingly, Dextran is a glucopyranose monomer-based biosynthetic polymer, which is strongly hydrophilic, chemically modifiable, biocompatible, stable in acidic and basic conditions, and commercially available in a variety of molecular weights. In particular, Dextran can serve as a surface coating material [62], which is able to be modified to have multiple pendant amine groups per chain, allowing it to be conjugated to carboxylated Pdots at multiple surface sites, thereby potentially cross-linking the Pdots to itself. In addition, Dextran functionalization further enhances the colloidal stability of Dex-Pdots across pH and ionic strength (Figure 2).

More specifically, a bifunctional tetrameric antibody complex (TAC) containing an antidextran antibody or antitargeted antibody was used to label biological targets with Dex-Pdots [64, 65]. TACs have been used in cell selection and isolation [63] but are not commonly used for fluorescence labeling. For example, Algar et al. used TAC-conjugated Dex-Pdots to demonstrate a proof-of-concept FLISA for human erythropoietin and selective labeling of human epidermal growth factor receptor 2 antigens on the surfaces of SK-BR3 breast cancer cells, in which dextran functionalization reduced nonspecific binding and TAC increased specific labeling [63]. Dextran functionalization is thus a promising strategy for increasing the stability of Pdots, enabling new bioconjugation methodologies, and improving their performance in bioanalysis and imaging. As a result, dextran functionalization is a promising strategy for overcoming some of Pdots' current limitations, such as low stability, nonspecific binding, and limited bioconjugate chemistry.

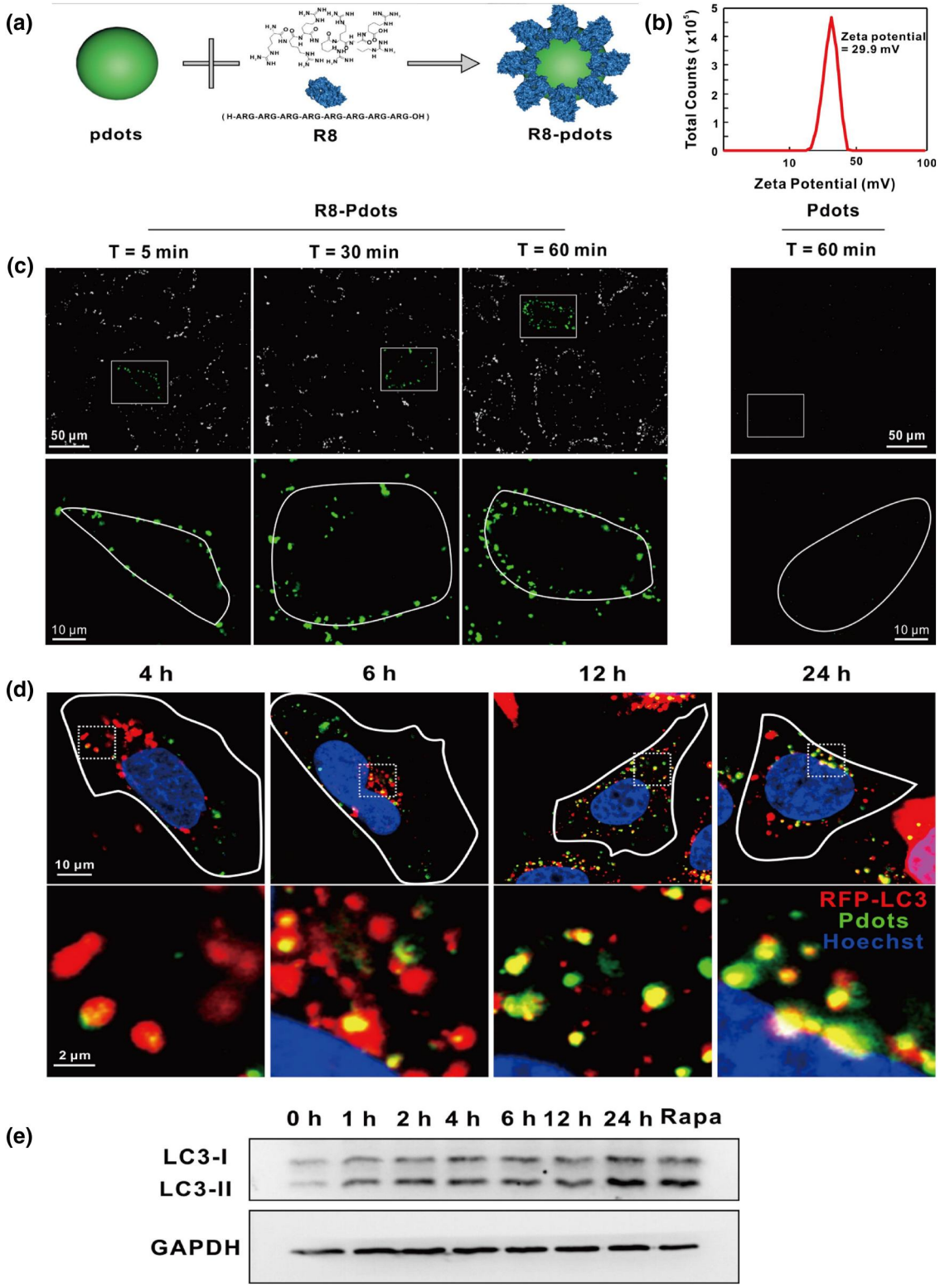

FIGURE 1 Biomodified polymer dots (Pdots) for live-cell imaging. (a) Schematic of as-prepared R8-modified Pdots by adsorption. (b) Zeta potential of R8-Pdots. (c) Time-dependent live-cell imaging with labeled R8-Pdots. (d) HeLa cells expressing RFP-LC3 (red) were incubated with 20 μg/mL Pdots (green) for confocal microscope at various time points. (e) HeLa cells were incubated with 5 μg/mL R8-Pdots at various time points. Cells treated with 100 μM rapamycin were included as a positive control. Protein levels of LC3 were analyzed by Western blotting, while GAPDH was included as loading control (adapted from reference [42] with permission).

2.3 | Biomodified Pdots for dynamic cell tracking

Due to the advantages of prolonged drug delivery, cell-based therapeutic and delivery systems have attracted considerable attention in recent years for future medical breakthroughs [66]. In addition to cell labeling, Pdots are also ideal platforms for cell tracking that are associated with cell-based therapy systems. For example, Wu et al. produced Pdots for in vivo cell tracking with long-wavelength excitation, NIR emission, and a high quantum yield [67]. By coating the Pdots with a cell-penetrating peptide, the labeling brightness of the cells ensured that they were effectively tracked in vivo in a dynamic way. In particular, they demonstrated that both stem cells and cancer cells labeled were captured within the body system. In addition, by using the same FL probes, they quantified the distribution of stem cells and cancer cells in vivo. When the same amounts (i.e., same brightness) of two types of cells were administered into mice, their results revealed distinct cell distributions and migration behaviors (Figure 3). The mice were then given 1 million labeled cells of both types through the tail vein. In vivo tracking confirmed that the two cell groups had different fluorescence distributions, in which the MSCs group's fluorescence remained relatively stable in the lung after 7 days, whereas the MCF-7 group's fluorescence showed an obvious tendency of the cells to be transferred from the lung to the liver during the first 4 days. These findings suggest that brightly FL Pdots are promising and dependable platforms for in vivo cell tracking and imaging applications.

2.4 | Biomodified Pdots for bacteria imaging and killing the bacteria

In recent years, extensive studies have been performed to construct various nanoplatforms for bacteria imaging and killing the bacteria. For example, Ning et al. developed a

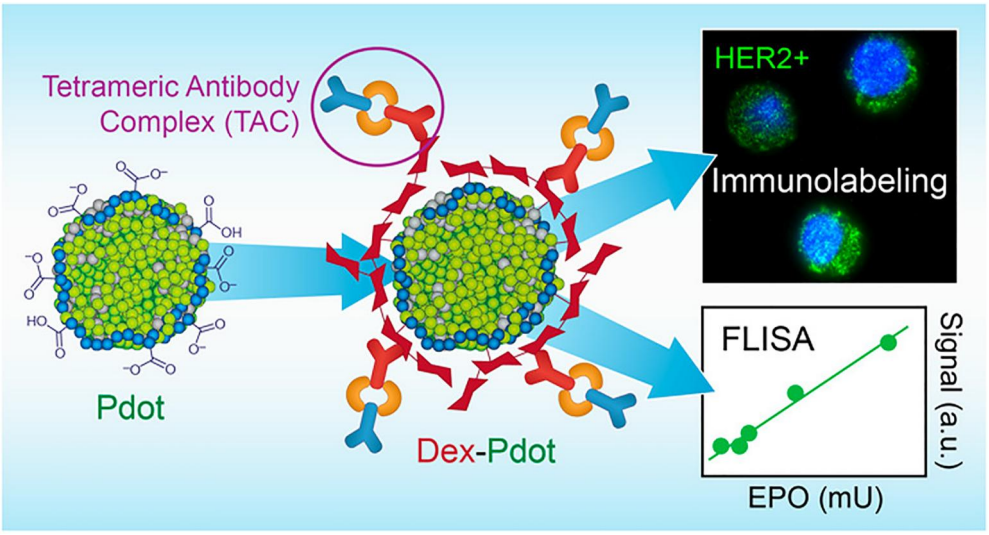

FIGURE 2 Schematic of Dextran functionalization of semiconducting polymer dots (Pdots) and conjugation with Tetrameric antibody complexes for bioanalysis and imaging (adapted from reference [63] with permission).

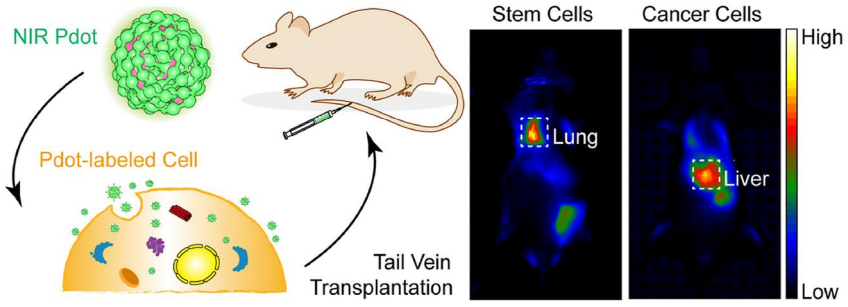

FIGURE 3 Schematic of labeling of cancer cells and stem cells via surface modification of polymer dots (Pdots), cellular uptake, in vivo tracking of the cells via tail vein injection, and in vivo analysis (adapted from reference [67] with permission).

family of maltodextrin-based imaging probes with good sensitivity and specificity for detecting bacteria in vivo [68]. Oosten et al. inspected the use of fluorescently labeled vancomycin for in vivo real-time imaging of bacterial infection with a human postmortem implant model [69]. In addition, Wang et al. recently demonstrated the use of a cationic poly(p-phenylene vinylene) derivative with polyethylene glycol side chains to selectively recognize, image, and kill bacteria in mammalian cells [70]. Meanwhile, due to their excellent photostability and thermal stability, bioconjugated Pdots are also good candidates for detecting and killing bacteria. Semiconducting polymers are compounds that, when exposed to light, can kill microbial cells by producing reactive oxygen species in the presence of oxygen [56, 57, 71, 72]. Importantly, it was discovered that a cationic-conjugated polyelectrolyte containing quaternary ammonium groups exhibited strong bactericidal properties [73–75]. For example, a cationic poly (p-styrene) derivative containing polyethylene glycol side chains was produced for bacterial detection and eradication [76]. Further, antibiotic-containing semiconducting polymers were used to selectively eliminate the bacteria and to identify specific bacterial cells using FL imaging. More specifically, the biolabeled Pdots produced can be used for concurrent imaging, photocide, and selectively identifying Gram-positive and Gram-negative microorganisms. Therefore, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were incubated with Van-Pdots and PB-Pdots, respectively [44, 77, 78]. Van-Pdots and PB-Pdots exhibited the capability to kill Van-sensitive bacteria *S. aureus* and PB-sensitive bacteria *P. aeruginosa*, respectively, under white light irradiation for 1 h. These findings demonstrated that certain bacteria can be selectively phototoxicated by biologically bound Pdots [44, 70].

3 | BIOMIMETIC PDOTS FOR TARGETED FLUORESCENCE IMAGING AND TUMOR TREATMENT

Theranostic nanoagents enable the detection of early stage disease, targeting of therapeutic agents, treatment of diseases, and monitoring of therapeutic efficacy in real time [13, 14, 20, 79]. However, the rapid RES clearance and low accumulation at the tumor site significantly limit their potential for clinical applications [46]. By contrast, an efficient biomimetic technique by using cell membrane coating is able to improve the targeting capability of nanoprobes for cancer detection and therapy [23, 80]. In particular, the adhesion proteins, antigens, and membrane structure of the source cell membrane can be reserved for the produced cell membrane-coated nanoparticles [81]. Therefore, cell membrane-camouflaged nanoparticles can acquire surface properties and functions similar to natural cell membranes. For example, red blood cell membranes have been used to camouflage perfluorocarbon, polymeric, silica, magnetic, and metal organic framework (MOF) nanoparticles for imaging-guided cancer radiotherapy and chemotherapy due to their inherent ability to enable immune evasion and prolonged blood circulation time [82–86]. Interestingly, it was discovered that cancer cell membranes (CMs) with a homologous binding process can improve the targeting delivery of MOF, iron oxide (IO), and polymeric nanoparticles into tumors [87]. Other tumor-homing cell lines, such as platelets, can also be used to coat IO nanoparticles for magnetic resonance imaging (MRI)-guided cancer phototherapy [88].

3.1 | Biomimetic Pdots for optical molecular imaging and tumor phototherapy

Semiconducting polymer nanoparticles (SPNs) can serve as contrast agents for NIR FL, chemiluminescence, and photoacoustic (PA) imaging and theranostic agents for phototherapy due to their structural plasticity [81–84]. For example, it was discovered that biomimetic SPNs coated with activated fibroblast (AF) cell membranes can be used for dual modal FL and PA imaging (PAI)-guided phototherapy [66]. A highly NIR-absorbing semiconducting polymer, poly(cyclopentadithiophene-alt-benzothiadiazole), and the AF cell membrane are used as the core and shell of an organic nanocamouflage known as AF-SPN. The SP functions as a theranostic agent generated not only NIR fluorescence and PA signals for imaging but also singlet oxygen and heat for combined photodynamic and photothermal therapy. Surface-coated AF cell membranes enable homologous targeting toward cancer-associated fibroblasts, promoting nanoparticle accumulation in tumors and finally improving photodiagnostic and phototherapeutic efficacy. Schematic of the mechanism demonstrates the principle of homologous targeting (Figure 4a). From PAI and fluorescence imaging, the biomimetic nanoparticle accumulation in tumor sites shows a better result (Figure 4b–e). AF-SPN preferentially targeted cancer-associated fibroblasts via the homologous targeting binding mechanism, resulting in higher accumulation in tumor tissues than both the uncoated and CM-coated counterparts. As a result, AF-SPN acted as the best phototheranostic nanoagents for tumor imaging and cancer treatment, providing amplified NIR fluorescence and PA signals and improving phototherapeutic efficiency. This study demonstrated an example of a cell membrane-coated biomimetic organic phototheranostic nanoagent that targets a component in the tumor

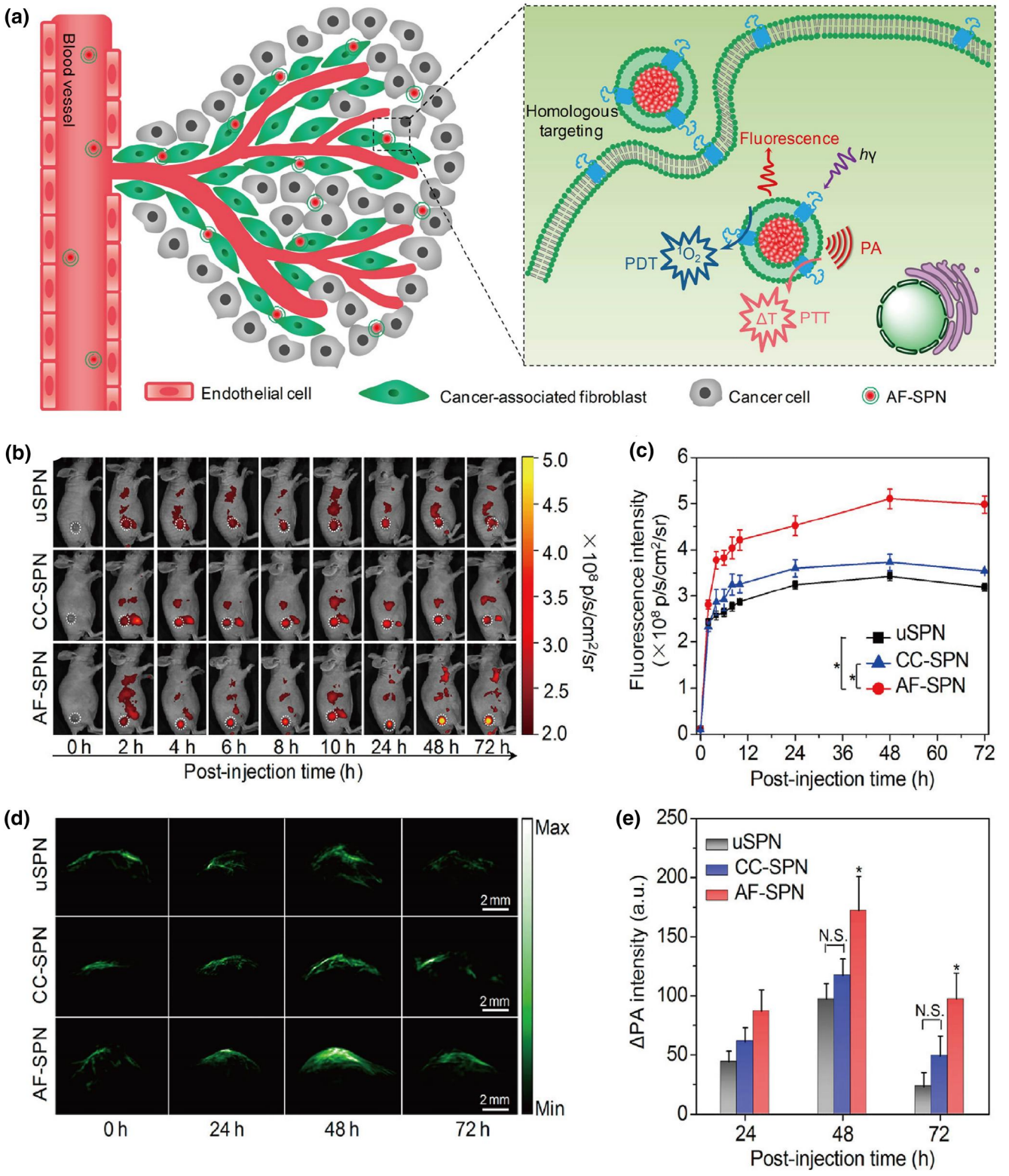

FIGURE 4 Biomimetic Pdots for tumor imaging. (a) Schematic of the homologous targeting of AF-SPN to fibroblasts for enhanced multimodal cancer phototheranostics. (b) FL imaging of 4T1 tumor-bearing mice in vivo at various time points with uSPN, CC-SPN, and AF-SPN, respectively. (c) FL signals at various time points with the three Pdots probes. (d) PA imaging of tumor associated with the three probes at various time points. (e) PA signal intensities at various time points (adapted from reference [45] with permission). AF-SPN, activated fibroblast-semiconducting polymer nanoparticle; CC-SPN, coated counterparts SPN; FL, fluorescent; Pdots, polymer dots; uSPN, uncoated uSPN.

microenvironment, which helps to design therapeutic strategies to overcome delivery barriers in tumors.

To date, tumor-targeting agents (e.g., aptamers, peptides, and antibodies) are able to recognize cancer cells' overexpressed surface antigens through ligand-receptor interactions [89–91]. However, cancer cells' inherent homologous adhesion property for tumor targeting is rarely inspected. Cancer cells expressing surface adhesion molecules with homologous adhesion domains (e.g., N-cadherin, galectin-3, epithelial cell adhesion molecule) in tumors have been shown to be responsible for multicellular aggregation formation [92]. Based on the mature technology of indocyanine green (ICG)-loaded lipid-polymer NPs, Cai et al. reported that CM-coated nanoparticles with ICG/poly(lactic-co-glycolic acid) core coated by cancer cell membranes (ICNPs) to synchronously recognize and eradicate tumors(Figure 5). Their findings showed that ICNPs not only have a homologous targeting effect at the cellular level, but they also have specific targeting ability at the animal level with high spatial resolution and deep penetration. ICNPs exhibit the potential to be an excellent nanoplatform for homologous-targeting dual-modal imaging and imaging-guided photothermal therapy. ICNPs might provide a versatile strategy for safe and effective cancer therapy by mimicking homologous cancer cells.

3.2 | Biomimetic Pdots for immunotherapy

In addition to traditional cancer therapeutic methods, such as surgery, chemotherapy, and radiotherapy, immunotherapy [93–95], including cytokine immunotherapy, blocking immunotherapy, chimeric antigen receptor T-cell therapy, and adoptive immunotherapy of T cells, has yielded promising results [96]. However, due to the challenging issues, such as tumor complexity, patient heterogeneity, and systemic immunotoxicity, immunotherapy cannot be applied to all cancer categories and clinical cases [97–99]. Therefore, it is essential to develop effective and long-lasting immunotherapy methods with tumor-specific immune responses without systemic toxicity. Interestingly, natural killer (NK) cells are innate immune cells that serve as the body's first line of defense against infection and cancer. As powerful effector cells, NK cells have received wide attention in the development of new drugs for tumor immunotherapy. More specifically, in antitumor immunotherapy, NK cells can induce pro-inflammatory M1 macrophage polarization and target tumor cells via proteins identified in NK cell membranes (e.g., RANKL or DNAM-1) [100, 101]. Likewise, NK cell membranes can also induce M1 macrophage polarization, stimulating the immune system during tumor immunotherapy. Cai et al. discovered that NK cell membranes can elicit tumor-specific immune responses by targeting cancer cells and inducing M1 macrophage polarization. In their study, NK cell membrane-decorated nanoparticles (NK-NPs) were used to improve the efficacy of NK cell membrane immunotherapy and ultimately achieve the desired treatment efficacy (Figure 6). Besides, shotgun proteomics was able to perform proteomic profiling of NK cell membranes, demonstrating that it allowed NK-NPs to target tumors, induce or enhance the polarization of M1 macrophages, and then generate an antitumor immune response.

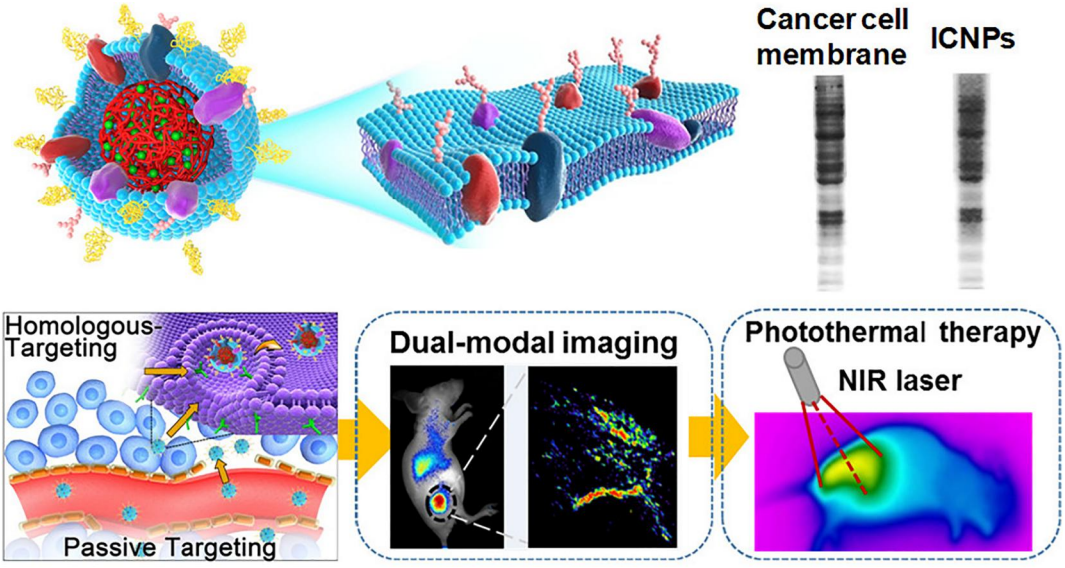

FIGURE 5 Schematic of the cancer cell membrane–biomimetic nanoparticles for targeting recognition of source cancer cell, dual-modal imaging, and photothermal therapy (adapted from reference [46] with permission).

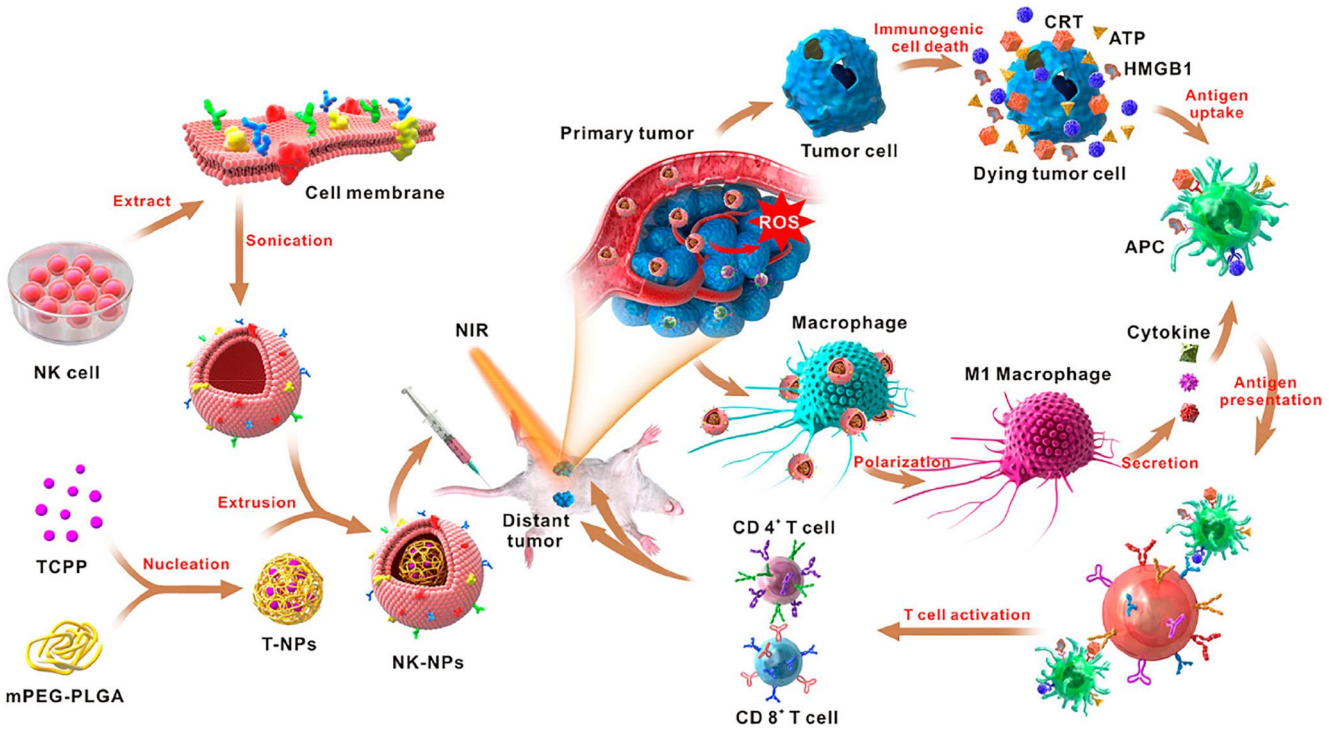

FIGURE 6 Schematic of NK cell membranes-cloaked nanoparticles for Photodynamic Therapy-enhanced cell-membrane immunotherapy (adapted from reference [48] with permission). NK, natural killer.

More importantly, NK-NPs-mediated Photodynamic Therapy (PDT) was able to improve NK cell membrane immunotherapy, which was capable of eradicating primary tumor growth, while also producing an abscopal effect to inhibit distant untreated tumors. Besides, NK-NPs-mediated immunogenic PDT might boost NK cell membrane immunotherapy efficacy, resulting in improved antitumor immunity that not only eradicated primary tumors but also inhibited the growth of preexisting distal tumors. As a result, the engineered NK cell-like Pdots might offer a versatile strategy for effective cell membrane immunotherapy.

3.3 | Biomimetic Pdots for brain tumor theranostics

3.3.1 | Pdots for GBM theranostics

Glioblastoma multiforme (GBM) is one of the most lethal primary central nervous system cancers in both adult and pediatric populations worldwide [102]. To date, sensitive and specific imaging of brain tumors in clinics has been hampered by a lack of efficiency in the targeted delivery of contrast agents toward tumor cells, which is a result of multifactorial constraints involving formidable BBB, blood–brain tumor barrier (BBTB), and complex brain tumor microenvironment [103]. BBB, which serves as a physical barrier to protect the brain from foreign substances in blood flow, is primarily composed of tight junctions by endothelial cells along the brain capillaries. Besides, BBTB refers to aberrant and excessive vascularization with dysfunctionally higher BBB permeability, which may favor theranostic agents traversing BBB as a result of pathological alterations caused by malignant cancerous cells [104]. A number of mechanisms, such as receptor-mediated transcytosis, have been proposed to actively and noninvasively cross BBB. Among other things, cyclic RGD (cRGD) has been identified as a highly effective peptide that can be attached to the surface of a nanomaterial and target the integrin v3 receptors that are overexpressed in the neovasculature. To address the issues caused by the brain tumor microenvironment, CM coating with homotypic targeting capability might be a promising strategy. For example, surgeons have used FI to differentiate tumor tissues by color codes to facilitate intraoperative microscopic identification and resection. However, due to the limited penetration depth of FI, only the outer layer of the tumor bulk was able to be imaged [105]. Additionally, PAI, which provides real-time images of tissues with a relatively deep penetration depth, has been proposed as a complementary imaging technique to capture the functional and structural information of brain tumor.

CP-based nanoparticles with intrinsic long-wavelength absorption and a large extinction coefficient have

been widely inspected as PAI contrast agents with high photostability, good biocompatibility, and strong PAI capabilities [106, 107]. To conduct MRI-FI-PA multimodal imaging, Liu et al. proposed using a cRGD-labeled brain tumor cell membrane as a "tactical shell" to improve brain tumor targeting and a multifunctional nanocomposite as the core (Figure 7) [48]. Metabolic engineering and bioorthogonal reactions enabled the decoration of cRGD onto the membrane of a brain tumor cell, allowing BBB crossing and homotypic targeting of brain tumor tissues [108, 109]. The nanocomposite core, which is made up of CP and ultrasmall IO nanoparticles, enables multimodal imaging in vitro and in vivo, demonstrating the potential of brain tumor targeting enhancement with the cRGD-labeled brain tumor cell membrane coating. In particular, cRGD-CM-CPIO has been validated as a high-performance imaging contrast agent for FI, MRI, and PAI using cellular uptake and mouse model experiments with significantly better brain tumor targeting capabilities than CM-CPIO. The reported work [49, 110–113] contributes to a better understanding of brain tumor targeting mechanisms by providing some insights on theranostic targeting of brain tumor cells from the standpoint of physiochemistry.

3.3.2 | Pdots for glioma imaging

The presence of the BBB in the glioma microenvironment results in low sensitivity in diagnosis, a poor prognosis, and low treatment efficacy [114]. As a result, the development of a multifunctional nanoplatform capable of crossing the BBB and targeting gliomas is critical for the high-sensitivity detection and ablation of cancer cells. Although Pdots-based FL imaging for glioma detection was carried out [110, 111, 115], as exogenous substances, they are easily recognized by the immune system and quickly cleaned by the liver and kidney [110]. Additionally, pure Pdots have difficulties in crossing BBB and specifically targeting brain tumor tissue. Therefore, to pass BBB and achieve a very accurate detection of brain malignancies, nanoparticles containing surface modified BBB-targeting ligands or cell penetrating peptides have been developed [48, 112]. More importantly, a unique approach for designing and synthesizing FL-based Pdots for glioma detection can be carried out by using the novel biomimetic nanoplatform coated with natural cell membrane For example, Pdots-C6 as biomimetic biomaterials for highly selective NIR-II (the second near-infrared window) FL imaging of gliomas was performed, demonstrating that Pdots-C6 had a homologous targeting capability at both the cellular and tissue levels with high spatial resolution and deep penetration (Figure 8). It was discovered that Pdots-C6 has great potential for clinical glioma diagnosis compared to pure Pdots due to their superior biocompatibility, highly targeting capability, and ability to cross BBB. As a result of their work, natural C6 membranes were successfully fused onto the surfaces of the Pdots, resulting in Pdots-C6 that perfectly integrates biomimetic function, high homotypic binding and glioma-targeting, and BBB crossing abilities. Pdots-C6 were created for enhanced NIR-II FI imaging of glioma via a homologous targeting mechanism due to improved Pdots delivery across BBB. When compared to Pdots, Pdots-C6-mediated NIR-II fluorescence imaging significantly improves imaging capabilities, resulting in high-accuracy glioma detection. These findings could lead to the creation of a biomimetic nanoplatform for the precise diagnosis of glioma.

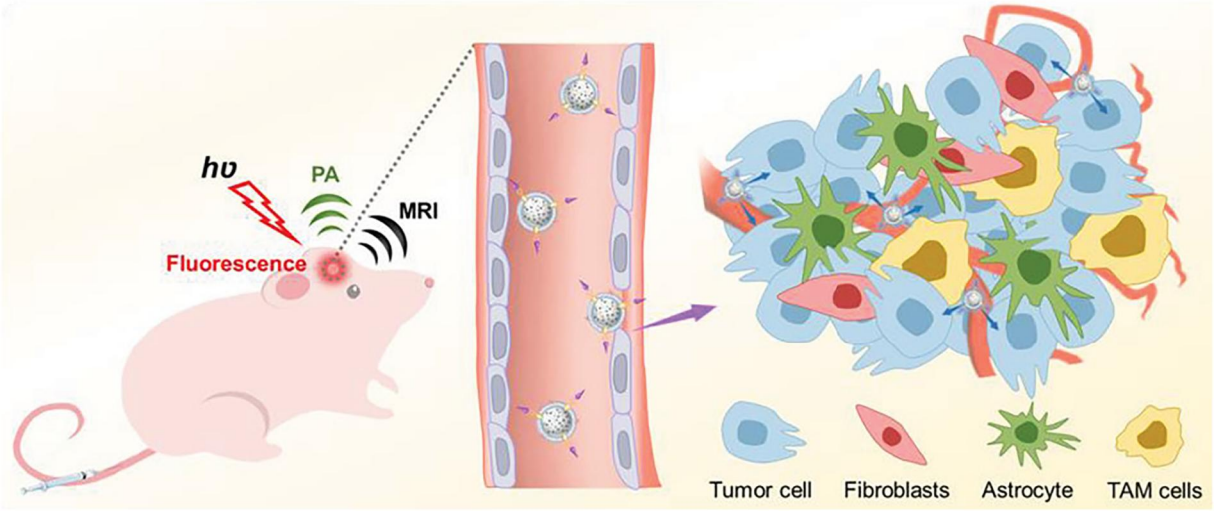

FIGURE 7 Schematic of the design of functionalized nanocomposites for blood–brain barrier penetration and navigation through the brain tumor microenvironment (adapted from reference [48] with permission).

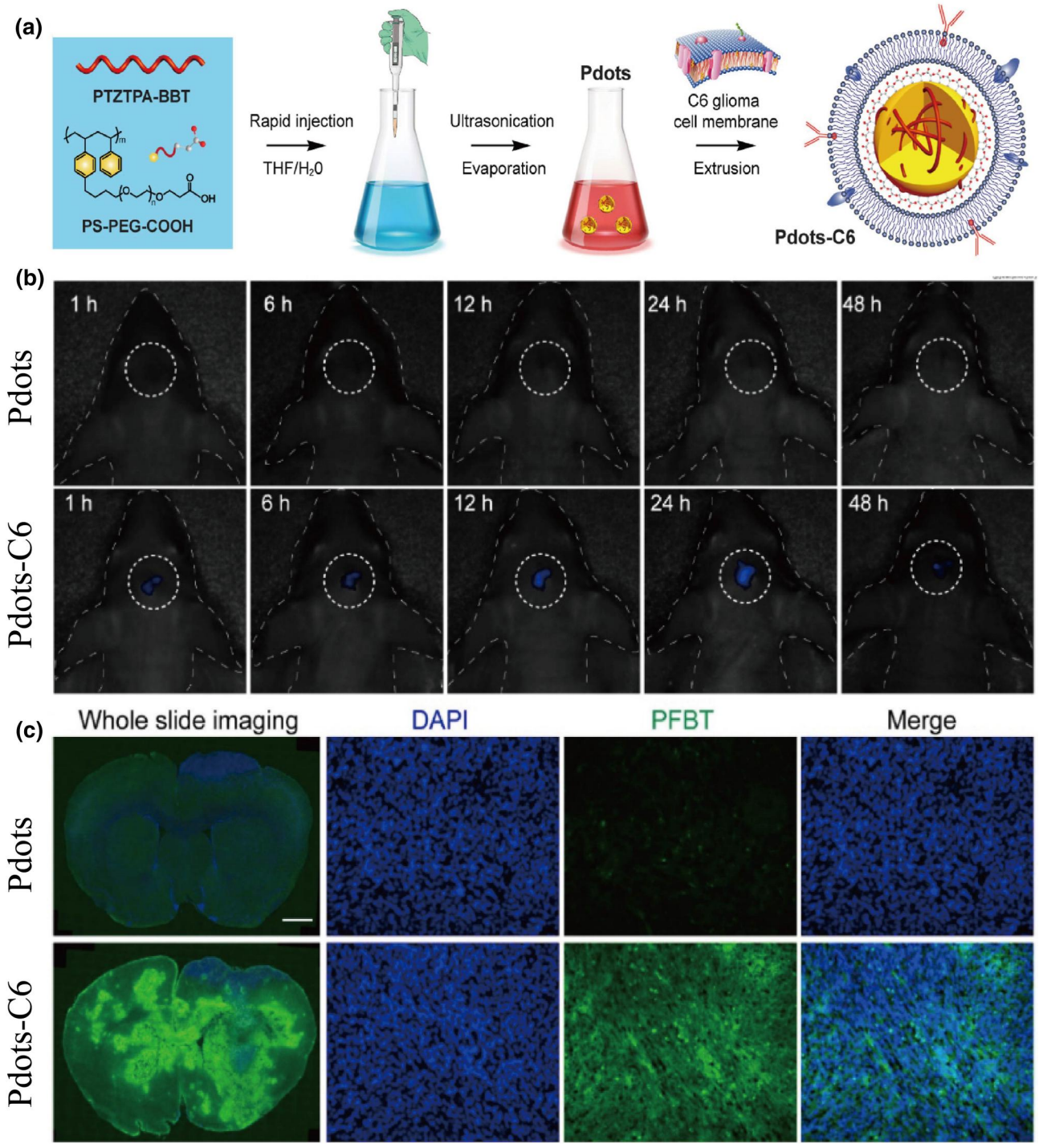

FIGURE 8 Biomimetic Pdots for glioma imaging. (a) Schematic of as-prepared Pdots-C6. (b) In vivo NIR-II Fl imaging of glioma at various time points with two Pdots and Pdots-C6, respectively. (c) Brain tissue 24 h postinjection. Scale bar = 1 mm (adapted from reference [16] with permission). NIR, near-infrared; Pdots, polymer dots.

4 | CONCLUSION AND FUTURE PROSPECTS

This review demonstrates that Pdots show the unbeatable advantages in efficiently targeted FL imaging and disease treatments using biological modifications. Briefly, the surface carboxyl groups in Pdots enable bioconjugation by the standard carbodiimide chemistry, whereas Pdots coated by cell membranes via electrostatic adsorption are able to target the leisure regions for disease theranostics. Although tremendous efforts have been made to optimize the functional properties of Pdots, several key issues still need to be addressed for future in vivo and clinical studies. First, the metabolism and clearance of nanoparticles due

to efficient accumulation in the body after treatment remain a challenge. Second, since more biofilm modifications can be linked to Pdots for imaging and cancer treatments, their potential side effects on normal tissues or various organs need to be further accessed in vivo before translation to clinical trials.

To be able to use this material in clinical medicine, when we verify its good biocompatibility and superior treatment effect in the laboratory, we have to pay attention to the final clearing of the material. For medicine, nanomaterials <5 nm will be cleared through the kidney system quickly. However, the modified biomimetic Pdots size is undoubtedly >5 nm, so they can circulate in the body for a long time and accumulate in the treatment area, which means that they must be degraded to eliminate. Commonly used degradation methods have pH changes [113], enzyme degradation, and oxidation-reduction process [116]. In the article quoted earlier, the tumor area usually meets the above degradation conditions. In some studies, we can also fully understand that the water-soluble conjugated semiconductor polymer can be decomposed into nontoxic molecular structures and discharged [117].

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

Not applicable.

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Not applicable.

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