

# Carbon Dot-Based Nanoparticles: A Promising Therapeutic Approach for Glioblastoma

Yongzhi Wang<sup>1,2\*</sup>, Hao Wu<sup>3,\*</sup>, Yu Guo<sup>4</sup>, Fangbao Li<sup>4</sup>, Hengzhu Zhang<sup>4</sup>

<sup>1</sup>Department of Neurosurgery, Fu Yang People's Hospital, FuYang, People's Republic of China; <sup>2</sup>Department of Neurosurgery, The Second Affiliated Hospital of Soochow University, Suzhou, People's Republic of China; <sup>3</sup>Department of Neurosurgery, The Second Affiliated Hospital of Xi'an Medical University, Xi'an, People's Republic of China; <sup>4</sup>Department of Neurosurgery, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, Yangzhou, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Hengzhu Zhang, Department of Neurosurgery, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, No. 98 Nantong West Road, Yangzhou City, Jiangsu Province, People's Republic of China, Email zhanghengzhu@sina.com; Yongzhi Wang, Department of Neurosurgery, Fu Yang People's Hospital, No. 501 Sanqing Road, Yingzhou District, Fuyang City, Anhui Province, People's Republic of China, Email wangyongzhi.369@163.com

**Abstract:** Glioblastoma (GBM) is a malignant tumor that currently still faces challenges for a complete cure. Although GBM treatment has made great progress, the prognosis of patients is still poor due to interference of various factors in treatment such as the blood-brain barrier (BBB), grade malignancy, intra- and intertumor heterogeneity, drug resistance, and poor targeting of anti-tumor drugs. In recent years, with marked advances in nanotechnology, different types of nanodrug delivery systems have been developed and have been considered as a promising therapeutic measure to gradually overcome chemotherapy resistance and improve tumor targeting. Carbon dots (CDs), as a new type of therapeutic NP, have become a research hotspot of concern for many researchers in recent years. NPs based on CDs have high modifiability and functionalization, allowing for covalent binding with chemotherapy drugs, genes, immune cells and photosensitizers, effectively targeting tumor cells and reducing peripheral cytotoxicity. However, at present, CDs are still in the basic research stage or the preclinical exploratory research stage, and has not yet entered the clinical trial stage or the implementation and application stage. Here, we review the fundamental principles of CDs in the broader field of nanotechnology, their development history, classification, synthesis, and potential for tumor treatment. Especially in the treatment of cancer, CDs can not only participate in photodynamic therapy, photothermal therapy, sonodynamic therapy, chemodynamic therapy, and chemotherapy, but also in multi-modal combination therapy. Here, we hope to provide some insights for further research.

**Keywords:** glioblastoma, cancer treatment, carbon dots, therapeutic approach

## Introduction

GBM is the primary brain tumor with the highest degree of malignancy. GBM is not only difficult to treat but also has a poor prognosis and a higher recurrence rate, accounting for approximately 70% of malignant brain tumors.<sup>1,2</sup> Based on the latest statistics from the World Health Organization, the median overall survival (OS) of patients with GBM is 12 to 16 months, and the 5-year OS rate is only approximately 5.6%.<sup>3</sup> Current treatment for GBM usually relies on standard combination therapy, including surgical resection, postoperative radiotherapy, and chemotherapy.<sup>4</sup> However, even with combination therapy, the median postoperative OS is only 10 to 16 months,<sup>5</sup> as surgery cannot completely eradicate tumor cells, and GBM cells have a strong ability for invasion, migration, and infiltration, leading to recurrence of GBM.<sup>6</sup> Therefore, in addition to traditional treatment methods, it is extremely urgent to explore several feasible alternative treatment strategies to effectively overcome the above issues, to improve postoperative quality of life, and prolong patient survival time. In recent years, with the rapid advancement of nanotechnology, nano drug delivery systems (NDDSSs) have been extensively researched, repeatedly verified and ultimately proposed for application in the treatment of GBM in different species.<sup>7</sup>

In recent years, carbon dots (CDs) have been favored by researchers due to their low-cost synthesis and raw materials, good solubility and stability, excellent biocompatibility, low toxicity and degradability. Nowadays, they have been widely applied in various fields, such as drug sensing, biomarker detection and cell biological imaging<sup>8–13</sup>. Today, as a novel treatment method, CDs based nanoparticles (NPs) offer a feasible direction and approach for anti-tumor therapy.<sup>14–18</sup> In this review, we summarize the development, characteristics, and anti-tumor mechanism of CDs NDDS proposed for the treatment of GBM.

## Research and Development History of Carbon Dots

Looking back on the development history of CDs, they have gone through a long process. With the advancement of technology and the efforts of generations of scientists, they have gradually evolved from fluorescent carbon dots to new nano-drug delivery systems based on carbon dots with multiple functions and application characteristics. CDs were first surprisingly discovered in 2004. It is a new type of coupled material with a diameter of only approximately 10 nm. With the technological advancements in functionalization and modifiers, CDs now have the advantages and potential to be developed into nanomaterial carriers with anti-tumor activity.<sup>18</sup> The development of CD has undergone three stages, namely, a discovery stage; an initial development stage; and a rapid development stage. The specific development process is as follows: Isolated fluorescent carbon in 2004; Surface passivation CDs in 2006; Fluorescent CQDs in 2010; Fluorescent GQDs in 2012; Fluorescent CPDs in 2013; Fluorescent  $\beta$ -C<sub>3</sub>N<sub>4</sub> Nanocrystals, Fluorescent chiral CDs, and Fluorescent C<sub>3</sub>N QDs in 2017; Fluorescent triangle CDs in 2018. Then CDs entered a rapid stage of development, and go deep into various fields (Figure 1).<sup>15,19,20</sup>

## Classification of Carbon Dots

Due to the multiple functions and roles of CDs, interestingly, they possess diverse appellations, such as carbon nanoparticles (CNPs), carbon dots (CDs), and carbon nanodots (CNDs). Multitudinous carbon-based nanomaterials have been delved and applied, such as carbon nanotubes (CNTs),<sup>15,20</sup> fullerenes,<sup>21</sup> graphene,<sup>22</sup> graphene quantum dots (GQDs),<sup>23</sup> CDs,<sup>24</sup> carbon nanocorners (CNHs),<sup>25</sup> carbon nanooxions (CNOs)<sup>26</sup> and so on. Among these, CDs have a huge potential development trend due to their unique biological properties.<sup>18,27–34</sup> In particular, CDs are more advantageous in medical applications.<sup>35,36</sup> The classification of CDs is shown in Figure 2.<sup>37</sup> Table 1 offers a comparison of CDs and other carbon-based nanomaterials.

## Design of Carbon Dots

Due to the issue of the emission wavelength of CDs itself, its penetration rate in biological tissues is relatively poor, which thoroughly impedes their application domains. Because of the objective existence of the above-mentioned issues, multifarious endeavors have been carry out to enhance and improve CDs functionality, for instance, methods such as doping with heteroatoms and surface passivation of materials and so on.<sup>13</sup> Most researches indicated that hetero-atom doping could be utilized to regulate and control the inherent traits of CDs. In addition, CDs are usually spherical in shape and have abundant functional groups on their surface, such as -OH, -COOH and -NH<sub>2</sub> (amine) moieties, which equip CDs with good bio-compatibility and good water solubility, and the ability to form new conjugations with different inorganic and organic substances.<sup>45,48</sup> Two types of CDs have been developed namely amorphous C-dots and G-Q-dots. The amorphous C dots are formed by simultaneous sp<sup>2</sup> and sp<sup>3</sup> hybridization of the carbon probes, which have the ability to undergo further surface modification. The G-Q dots possess hybrid sp<sup>2</sup> nanocrystalline carbon nuclei, an asymmetric structure due to abundant N and O groups that perturb the carbon structure (Figure 3).<sup>49</sup>

## Emerging Applications of Carbon Dots

In recent decades, research regarding the synthesis, characteristics and biological applications of CDs possess grown in a spiral. In terms of size and photoluminescence performance, CDs have a high degree of similarity to quantum dots (QDs). However, compared to QDs, CDs are relatively innocuous.<sup>50</sup> CDs achieve relatively uniform dispersion, better stability, and biocompatibility.<sup>51</sup> In addition, the fluorescence characteristics and plentiful surface functional groups of CDs allows them to be relatively easily modified or further functionalized.<sup>52</sup> Combined with relatively better biocompatibility and excellent

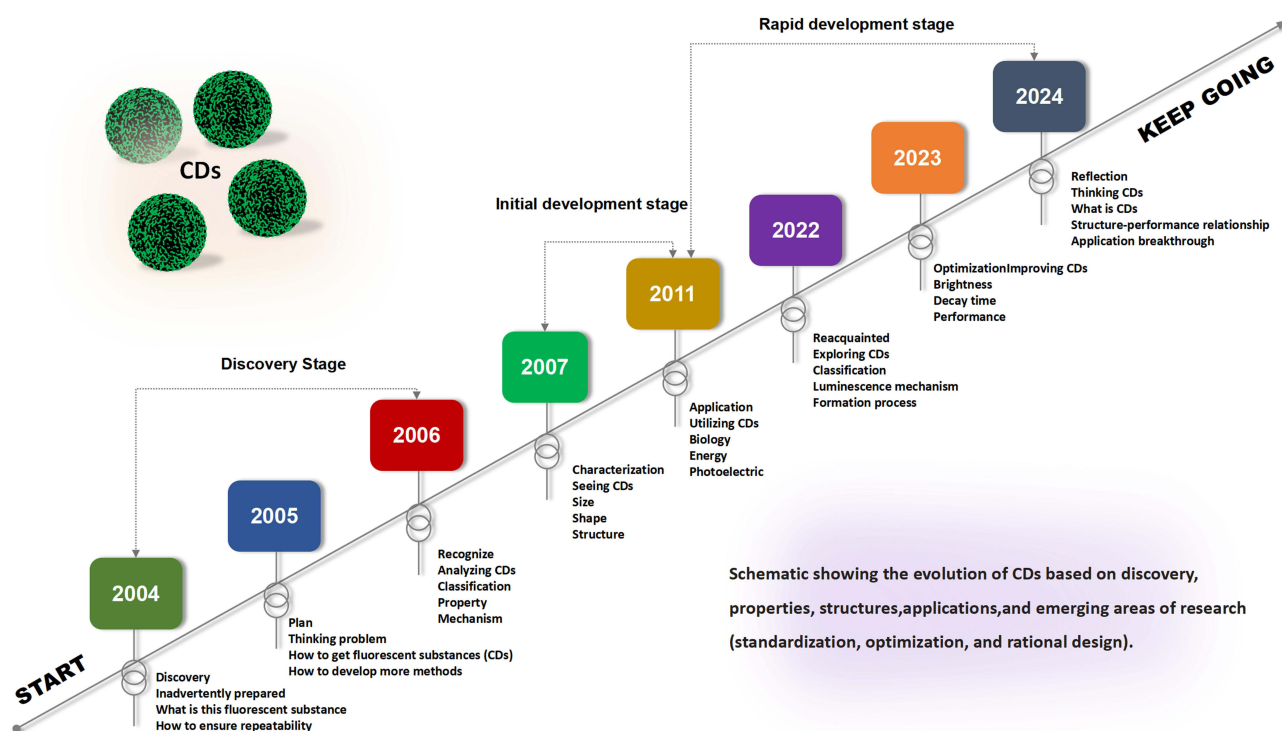


Figure 1 Research and Development History of CDs.

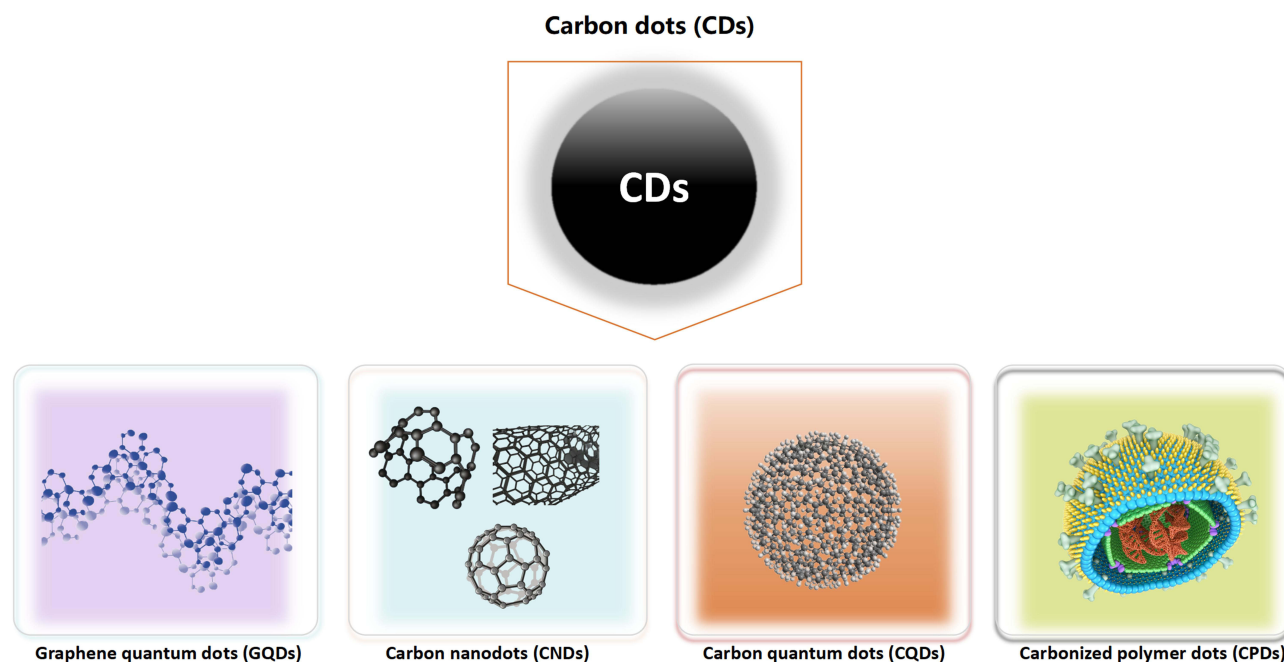


Figure 2 Classification of CDs.

stability, CDs have been involved in many research fields and have received much attention, for example, in optical, energy, and biological applications, especially for the treatment and diagnosis of cancer, such as analysis of pharmaceuticals and biomarkers, cellular bio-imaging (in-vitro and in-vivo bio-imaging),<sup>13</sup> medical imageology, nanomedicine, drug/gene delivery, gene-targeted combined therapy, PDT, PTT, and as antibacterial agents<sup>53–56</sup> (Figure 4)

**Table 1** Comparison of CDs and Other Carbon-Based Nanomaterials

Type	Traits	Applications	Limitations	Refs
Graphene	Comprises one atom-thick carbon (sp <sup>2</sup> hybridized) sheets of six-member rings, providing an exposed surface area that is nearly twice as large as that of SWCNTs	Comprises one atom-thick carbon (sp <sup>2</sup> hybridized) sheets of six-member rings, providing an exposed surface area that is nearly twice as large as that of SWCNTs	Absence of metallic impurities that can affect accuracy of sensor; commercial availability of graphene and graphene platelets is limited	[38,39]
CNTs	Unique combination of stiffness, strength, and tenacity compared with other fiber materials; high thermal and electrical conductivity	Can reach cytoplasm and nucleus through the lipid bilayer, thus have potential use in biosensors, biomedical devices, and drug delivery; greater ability of conjugation with various bioactive agents, such as peptides, proteins, nucleic acids, and therapeutic agents; greatest stability of nanocarriers	Severe toxicity in cultured cells, such as human keratinocytes, T lymphocytes, kidney cells, alveolar macrophages, and endothelial cells in vitro; reproduce cellular oxidative stresses, thus incompatible with biological systems; insoluble in most common solvents.	[40–42]
GQDs	Strong and tunable photoluminescence; A high loading capacity of aromatic compounds and release properties; The ability to absorb incident radiation	Fluorescence bioimaging and biosensing; Diagnostic Platforms; Drug /gene delivery; Photodynamic Therapy;	Toxicity and clinical practical application	[43,44]
CDs	Zero-dimensional nanocarriers with diameter<10nm; spherical nanocrystal design; synchronized sp <sup>2</sup> and sp <sup>3</sup> hybridization	Used for targeted drug and gene delivery, tumor targeting, monitoring of cellular trafficking, and diagnostic imaging	Poor stability (the stability after modification/ functionalization is better); difficult to maintain properties for long periods of time	[45–47]

## CDs Synthesis

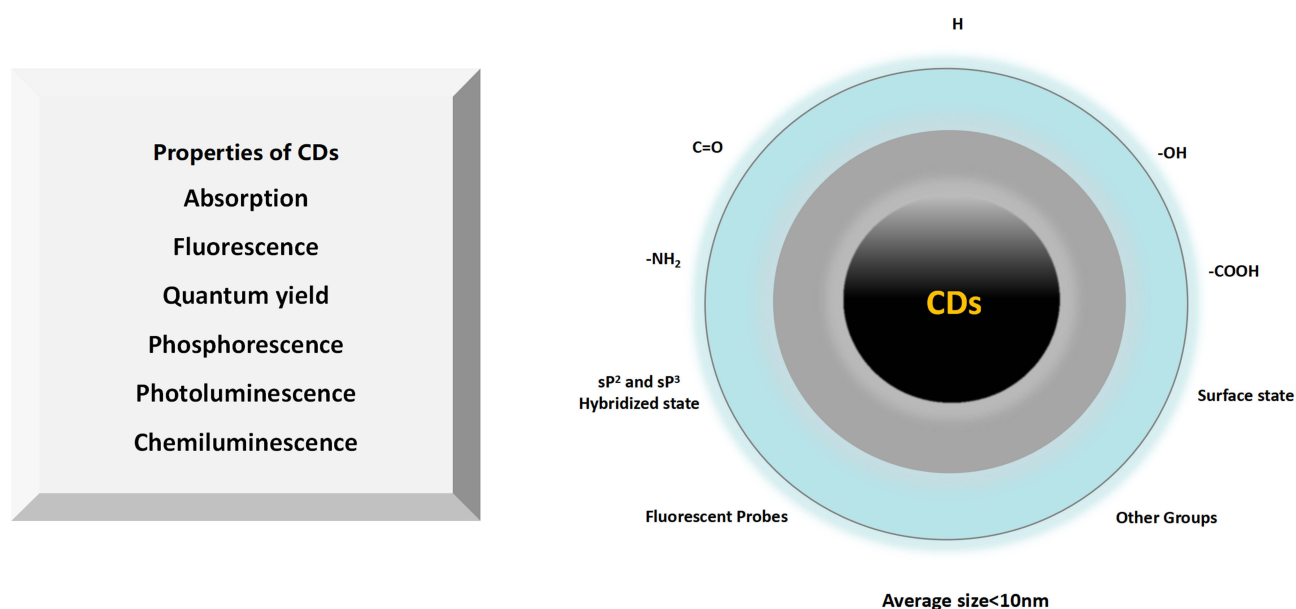
Under normal conditions, the synthesis of CDs requires multifarious chemical substances and biological groups, such as –COOH (carboxyl groups). Because of the existence of carboxyl group, CDs have good solubility. The presence of functional groups gives CDs features that can be further modified or reassembled. Two common synthetic methods for the preparation of CDs<sup>8</sup> are illustrated in Figure 5. That are top-down and bottom-up means. The first technique mainly include laser ablation, arc discharge and high energy ball milling. But above ways utilize strong chemical reagents and tedious conditions for synthesis.<sup>42</sup>

The second technique primarily contains hydrothermal/solvothermal synthesis, pyrolysis and electrochemical methods. However, the most crucial deficiencies of the bottom-up synthesis technique is its relative complexity, as special experimental instruments are required during the synthesis process and it takes a relatively long time.<sup>57</sup> The formation of amide bonds is generally accomplished by covalent modification between the CD carboxyl group and the primary amine by EDC/NGS coupling chemistry (Figure 6).<sup>57–59</sup>

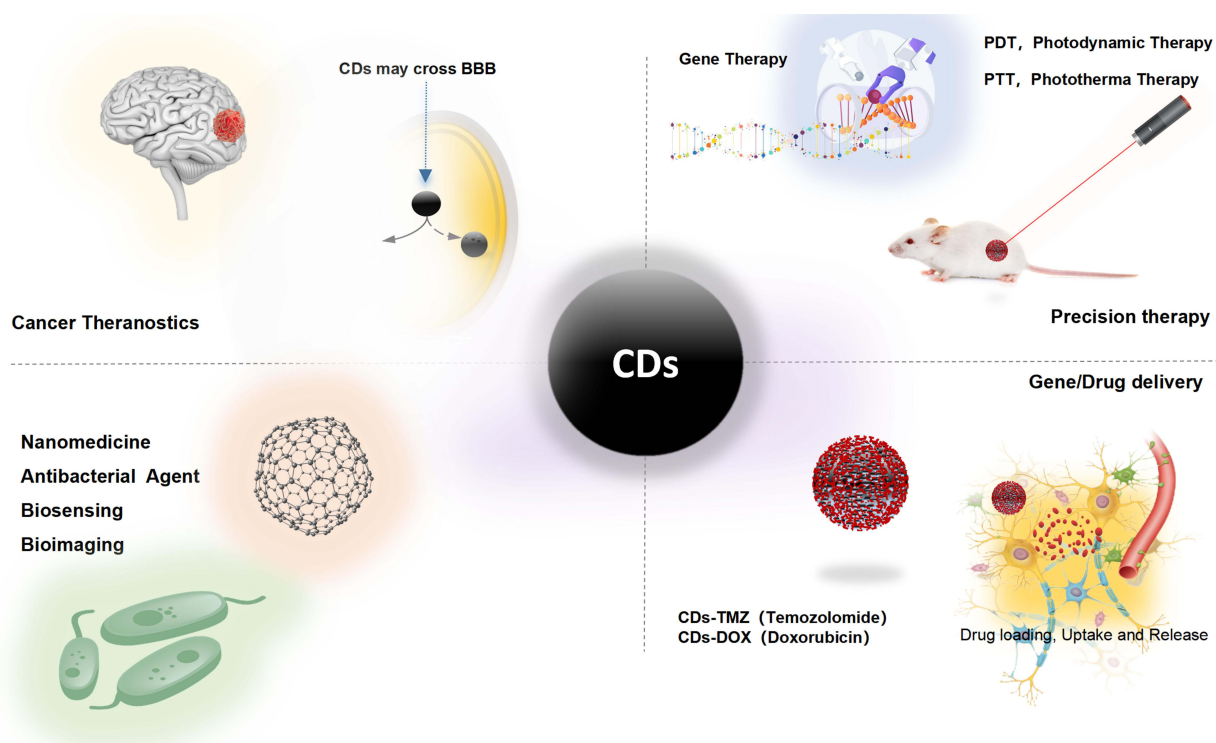
## CDs-Relevant Toxicity and Remedial Methods

Before the application of CDs, its toxic effects in organisms must be considered and verified. Table 2 summarizes the toxicity verification of CDs in vitro. Studies have confirmed that PEG-modified CDs can significantly reduce their own toxic effects and thus can be used in the fields of biological imaging and medical exploration. Although in vitro studies have shown that CDs is non-toxic or low-toxic, we still cannot be blindly optimistic. Because, up to now, there are still relatively few experiments on in vivo toxicity researches (Table 3), lacking reliable data to support and verify the toxic





**Figure 3** Design of CDs with different surface functional groups.

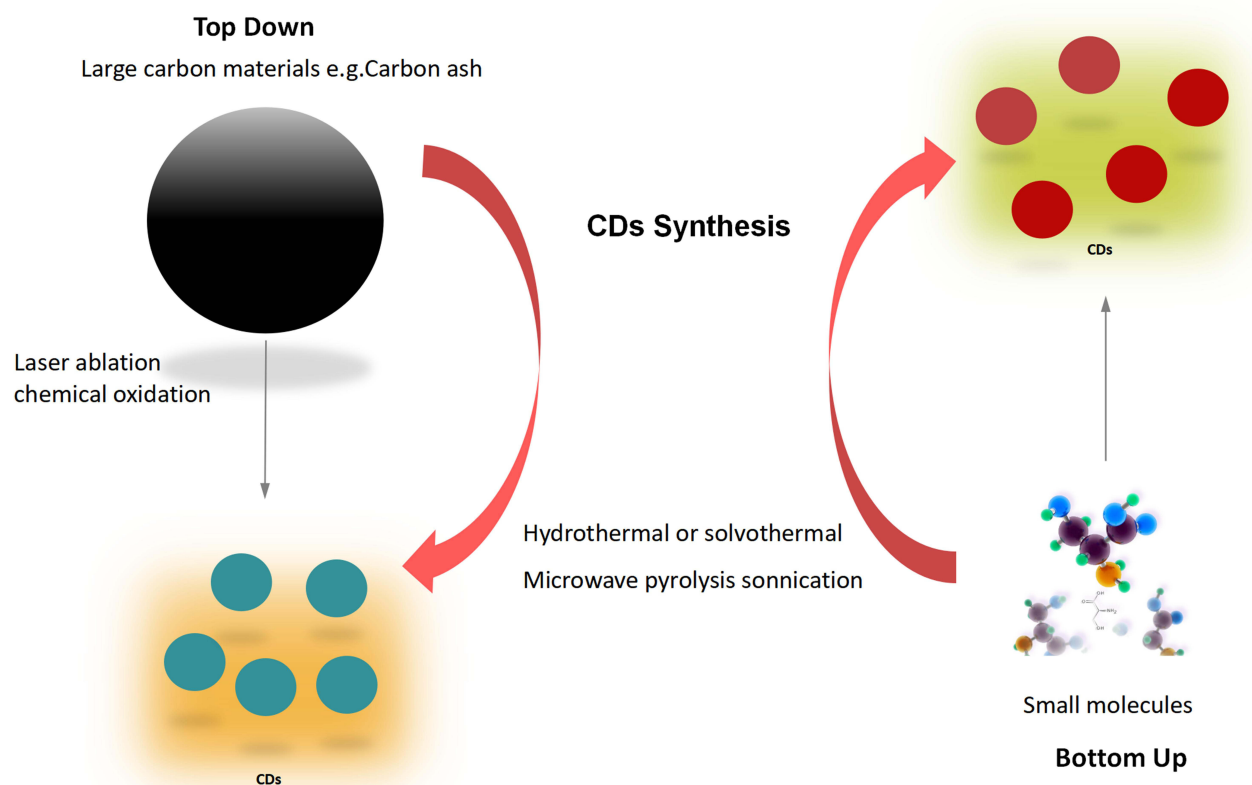


**Figure 4** Emerging applications of CDs.

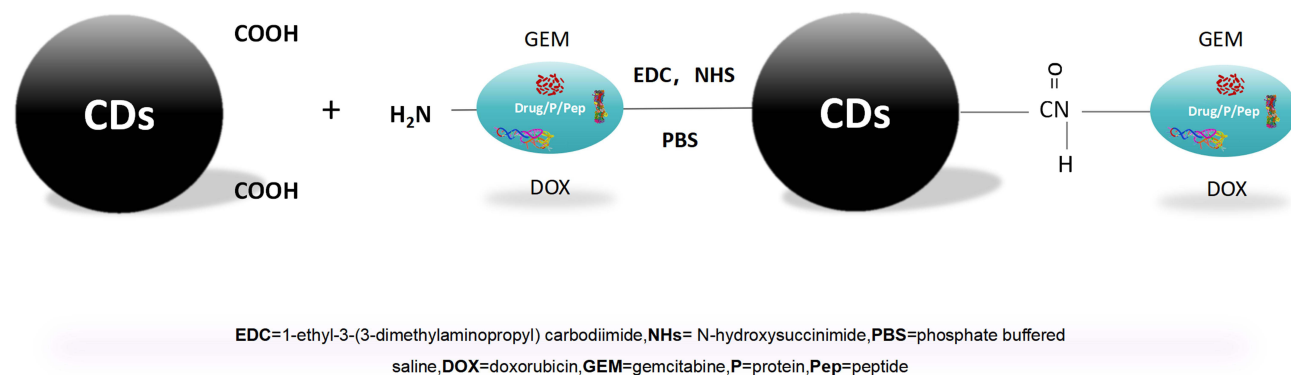
effects of CDs. However, we firmly believe that with technological innovation and the improvement of functionalization, more experiments will focus on toxicity verification in organisms.

## How to Enforcing Remedies for Weakening Toxicity

It is well known that high molecular polymers such as polyacrylic acid (PAA) and branched-chain polyvinylimide (BPEI) themselves have certain toxic effects on living organisms. For instance, the exposure time of free PAA to CDs is at least



**Figure 5** Two synthetic methods “top-down” and “bottom-up” are common for the preparation of CDs.



**Figure 6** Simplified scheme depicting the conjugation of CDs to a chemotherapeutic agent.

about 10 hours or more, or even longer. Due to the inevitable toxic effect, it will cause a certain degree of damage to cells. But how to reduce this toxic and side effect? This is a fatal problem. Experimental research has proved that the remedial measures for toxicity mainly involve shortening the cell incubation time and exposure time, using the minimum concentration of drugs or materials, and innovating technologies, including the modification of physical and chemical properties and surface functionalization techniques. Although the toxicity of CDs is relatively low, it can still be further reduced through the intervention of the techniques mentioned above. At the same time, it can also be fully modified by using polymers PEG (polyethylene glycol) with good bio-compatibility and amino acids, etc.

**Table 2** In Vitro Toxicity Researches of CDs

Method	Source	Size	Surface	Cell line	Monitoring	Refs
Laser ablation	I3C powder and graphite cement	4–5nm	Polyethylene glycol -1500N	MCF 7 cell	Increased cell viability	[60]
Hydrothermal therapy	Polyethylene glycol	2–4nm	/	Hep G2 cell	Cell viability: At 100 mg/mL: 90% At 400 mg/mL: 49%	[61]
Hydrothermal therapy	/	/	Pyridinic-N pyrrolic-N	U-87 MG brain cells	/	[62]
Hydrothermal therapy	Citric acid and 1,2-ethylenediamine	1–4.5nm	/	NIH 3T3 cells, HEK293 cells, HeLa cells, and MCF-7 cells	Cell viability At 0.25 mg/mL NIH 3T3 cells: 95% HEK293 cells: 92.4% HeLa cells: 97.6% MCF-7 cells: 95.9%	[63]
Hydrothermal Carbonization	Linear PEI and citric acid	/	Polyethy lenic amine analog, 1,2-ethylenediamine, Diethylenetriamine, Tetraethylenepentamine	HeLa cells	Cell viability: At 800 mg/mL: 90%	[62]
Heat reflux approach	L-glutamic acid	5.42nm	Polyethylene glycol 200	CT26WT and CAL-27T cells	Cell viability: At 0.1–1 mg/mL CT26WT: 82% CAL-27T Cells: 60%	[64]
Polymerization method	$\alpha$ -cyclodextrin	70–80nm	Hyperbranched polyglycerol using grafting method	A549cells	Cell viability At 0.1 mg/mL 90%	[65]

**Table 3** In Vivo Toxicity Researches of CDs

Method	Source	Size	Surface	Model	Monitoring	Refs
Laser ablation	I3C powder and graphite cement	4–5nm	Polyethylene glycol 1500N	Mice	24 hours later, low accumulation 28 days later, No monitoring toxic action	[60]
Mixed acid therapy	SWCNTs, MWCNTs and graphite	3–4nm	/	Mice	Nontoxic, No weight loss, or death of mice	[64]
Nitric acid oxidation	Raw soot	1–3nm	Polyethylene glycol 2000N	Mice	No abnormalities or gene toxicity	[65]

## Carbon Dots Based Nanoparticles for Photothermal Therapy of Tumors

In recent years, PTT has been widely applied in the research of cancer treatment. Its principle is to convert light energy into heat energy to deal a devastating blow to tumors. However, a crucial factor remains to be determined, that is, how to ingeniously design synergistic NPs as potential photothermal transducers that can truly and effectually improve the efficacy of PTT in killing tumor cells. On this basis, some researchers have strategically designed, prepared, and characterized hollow Cu NPs (CuSCDs). These NPs displayed excellent photothermal conversion efficiency, enhanced biocompatibility, and reduced toxicity under 808 nm laser irradiation. After coating a CuSCD-loaded proteasome inhibitor with the hybridized macrophage cell membrane of the T7 peptide, CuSCDB@MMT7 achieved specific targeting of cancer cells, immune escape, and boosted endocytosis. In general, CuSCDB@MMT7-triggered PTT

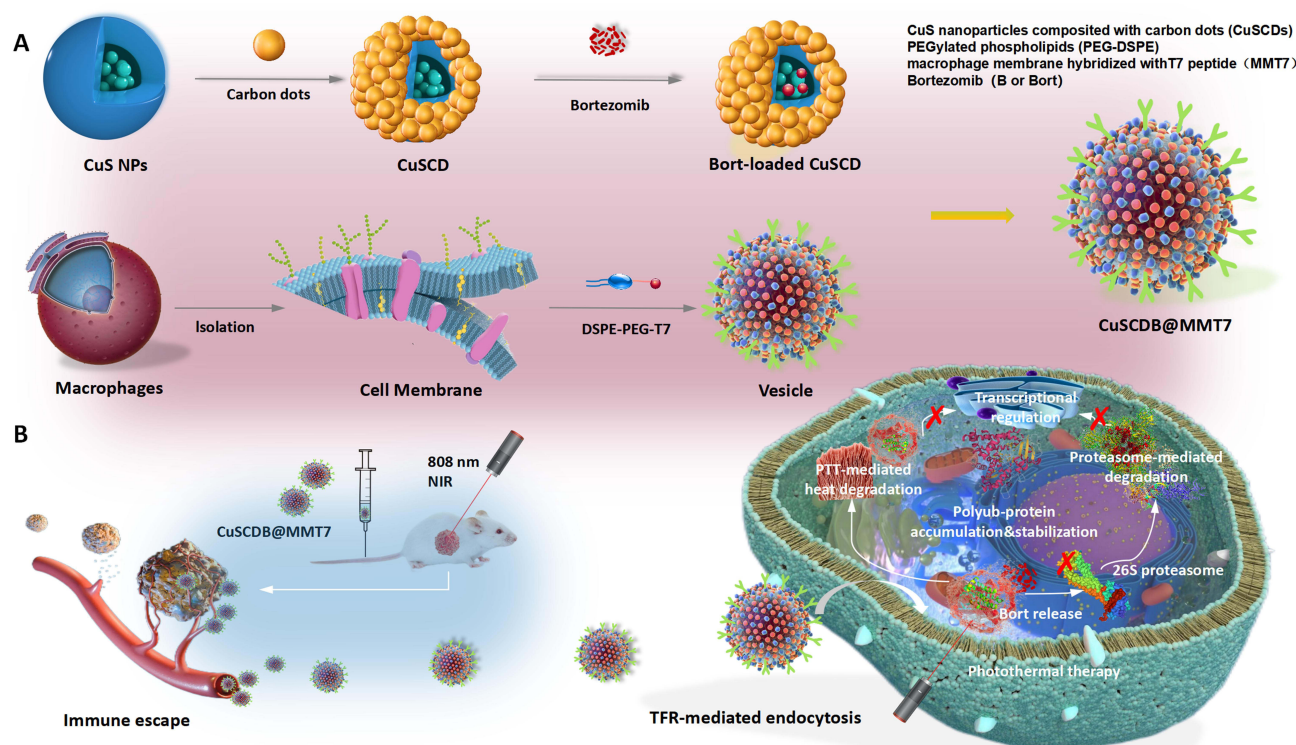
displayed the accumulation of polyubiquitinated tumor suppressor protein, which was thermally steadied at a high temperature induced by near-infrared light, enhancing apoptosis and decreasing tumor cell metastasis. Through a series of characterization monitoring, the results indicated that CuSCDB@MMT7 possessed high stability, with relatively considerable loading and encapsulation efficiency of 20.5% and 81.9%, respectively. Meanwhile, the monitoring manifested that under laser irradiation, the temperature of CuSCD can rapidly accomplish above 90°C without obvious attenuation, and the heat generation capacity can be maintained at a certain steady-state level. More importantly, the research suggested that CuSCDB@MMT7 can specifically target tumor cells and has the ability to evade immunity. Laboratory monitoring demonstrated no obvious signs of damage to the liver and kidneys, which provided strong evidence for clinical transformation. It is gratifying that CuSCDB@MMT7 can accumulate effectively at tumor sites and manifest an increasing trend over time, further confirming that CuSCDB@MMT7 can accumulate at tumor sites via EPR and active targeting.

The above studies provide strong evidence for the PTT strategy of Cu/CDs nanocomposites loaded with proteasome inhibitors and highlight a promising therapeutic strategy that can achieve effective clinical cancer treatment (Figure 7).<sup>66</sup>

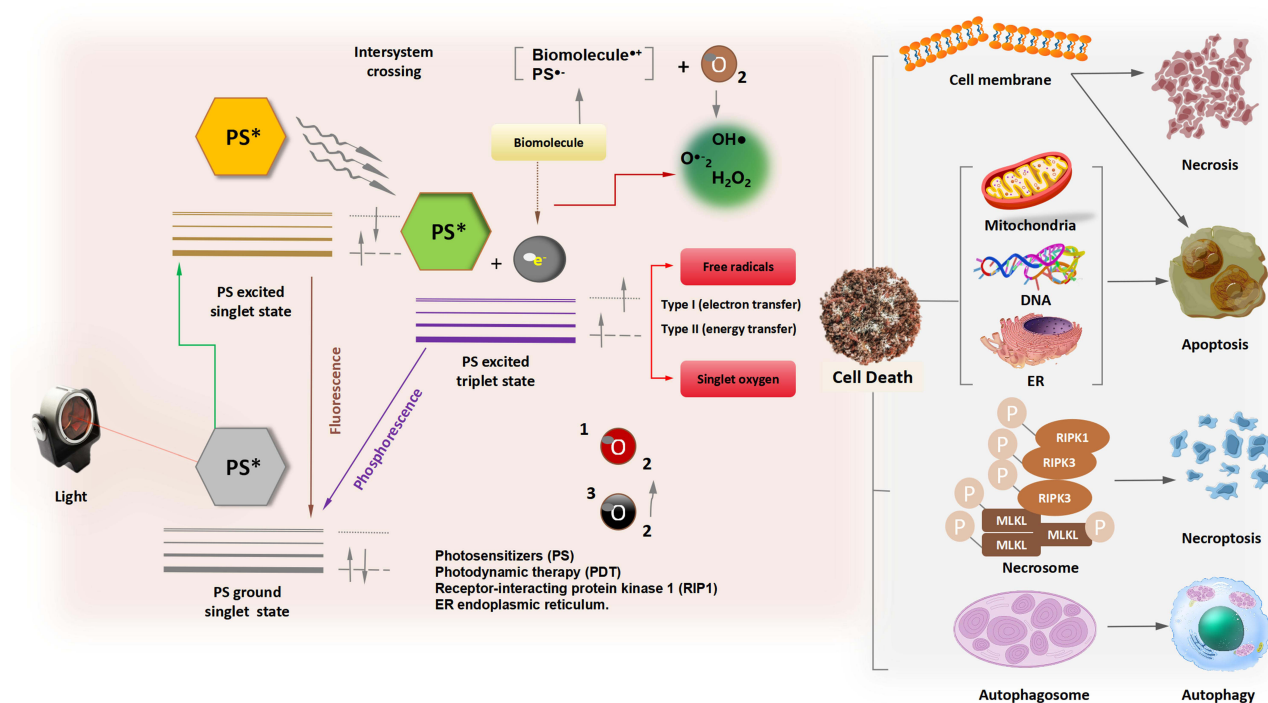
In summary, the evidence to date strongly supports nanodrug delivery system designed based on CDs has a very good prospect for the destruction of tumor cells.

## Therapy and the Principle of Carbon Dots in Photodynamic Therapy

The characteristics of PDT are determined by three key elements: light source, PS, and O<sub>2</sub>. The principle of the reaction is that when the light source is irradiated, PS absorbs energy from the ground phase to the excited phase and reacts to further produce reactive oxygen species (ROS), which in turn destroy cancer cells.<sup>67</sup> When PS receives a certain amount of light and absorbs a certain amount of energy, it changes directly or indirectly from the ground state to the excited state, and then two types of reactions can occur. The first reaction, the Type I reaction, involves the generation of hydrogen peroxide, superoxide anion, and hydroxyl radical.<sup>68</sup> The second reaction, type II, differs from the first by producing <sup>1</sup>O<sub>2</sub> directly through an “intersystem crossing” process (Figure 8).<sup>69</sup> When the two types of reactions occur simultaneously,



**Figure 7** (A) Schematic illustration of the generation of proteasome inhibitor-encapsulated CuS/CDs nanocomposites (CuSCDB@MMT7). (B) Schematic illustration of the application of CuSCDB@MMT7 for enhanced PTT via heat-stabilization of various substrates in the ubiquitin-dependent proteasomal degradation pathway.



**Figure 8** Schematic illustration of photodynamic reactions (either type I or type II) and cell death pathways in the process of PDT.

the resulting  $H_2O_2$ ,  $O_2^-$ ,  $\bullet OH$ , and  $^1O_2$  are defined as ROS.<sup>69–73</sup> The Type III reaction mechanism involves a direct and efficient destruction of biological target molecules.<sup>74</sup> First, when CDs are activated by a light source, the absorbed electron energy is excited from  $S_0$  (ground state) to  $S_1$  (singlet state), and second, the energy is released through three routes and returned to a relatively lower energy level (Figure 9). The first route is nonradiative emission: that is, return from  $S_1$  to  $S_0$  as heat. The second route is radiative emission that involves phosphorescence and fluorescence, radiative processes in which energy relaxation occurs and in which energy is released in the form of electromagnetic radiation light. The third route is to transition from  $S_1$  to the excited state  $T_1$  via an intersystem crossing (ISC). The process in the third route is related to the ability of  $T_1$  to initiate a radical chain reaction (type I) after transferring electrons and  $O_2$  to the reaction substrate and further forming ROS such as  $H_2O_2$ ,  $O_2^-$  and  $\bullet OH$ , or it may acquire  $^1O_2$  by transferring energy to  $O_2$  and extracting electrons from some groups (such as aromatic rings and phenols) to produce a ground state via CDs (Type II). The three key free radicals ( $H_2O_2$ ,  $O_2^-$ ,  $\bullet OH$ , and  $^1O_2$ ) generated by the two approaches in the third route above are the significant factors for CDs to implement the PDT effect.<sup>75–78</sup> The  $^1O_2$  generated by type II reaction is generally considered the most important factor responsible for the efficacy of PDT.<sup>79</sup> However, hypoxia that can occur in malignant neoplasms, such as in GBM, may reduce the antitumor effects of type II PDT. Hence, type II PDT is more suitable for tumor environments with  $O_2$ .<sup>80,81</sup> Although type I PDT is relatively better suited to anoxic environments, as it generates lower cytotoxicity due to  $O_2^-$  and  $H_2O_2$ .<sup>82,83</sup> Hypericum perforatum has been applied to overcome these issues and achieve the control of Type I and Type II PDT. Researchers synthesized three red carbon dots (RCDs), which possess similar core structures and diverse surface states, resulting in various  $\Delta E_{S_1-T_1}$ . However, a smaller  $\Delta E_{S_1-T_1}$  is more favorable for energy transfer from  $S_1$  to  $T_1$ , resulting in more  $^1O_2$  production. Moreover, since the three RCDs have the same REDOX potential, the same  $O_2$  is produced (Figure 10).<sup>84</sup>

There are three key mechanisms by which PDT eliminates tumor cells: the first is to promote apoptosis and necrosis of tumor cells by inducing oxidative stress; the second is to cause vascular injury, and the final mechanism is to trigger an autoimmune and inflammatory response.<sup>85</sup> In general, the key active treatment of PDT is to promote tumor cell apoptosis.<sup>86</sup> To further evaluate the mechanism by which sulfur-doped carbon dots (S-CDs) conquer tumor cells, researchers took advantage of a Fluo-4 AM ( $Ca^{2+}$  probe) to calculate the effective concentration of  $Ca^{2+}$  entering



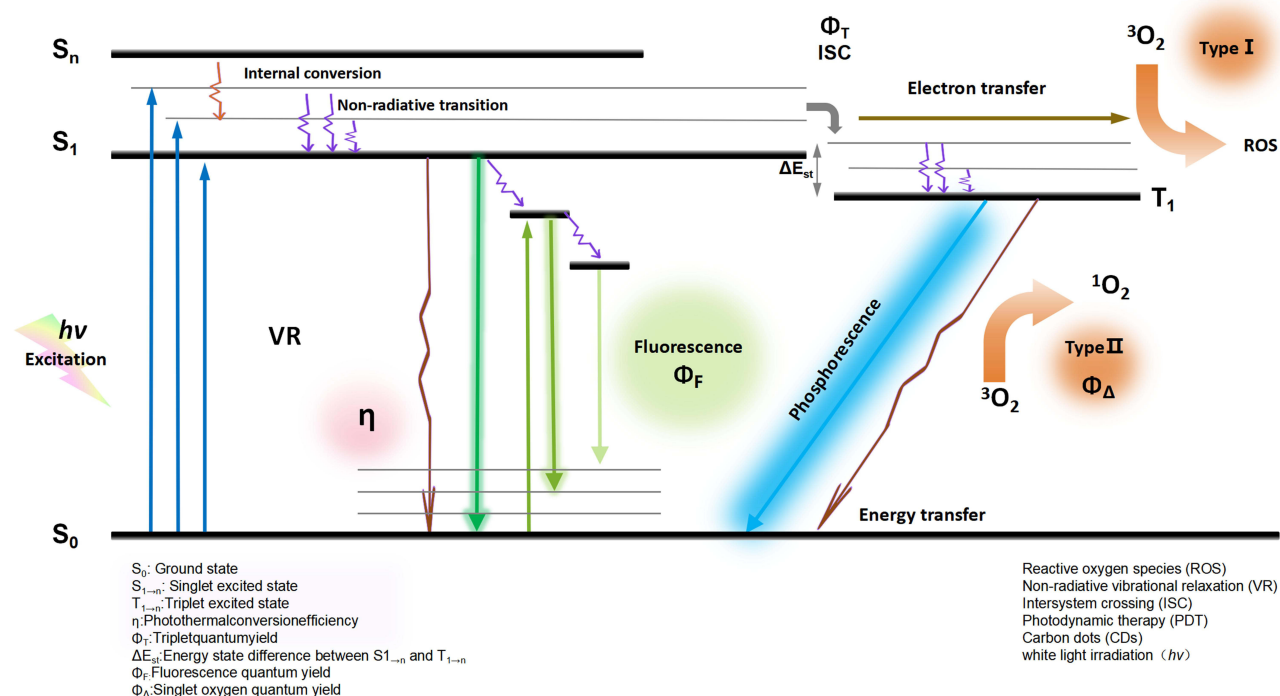
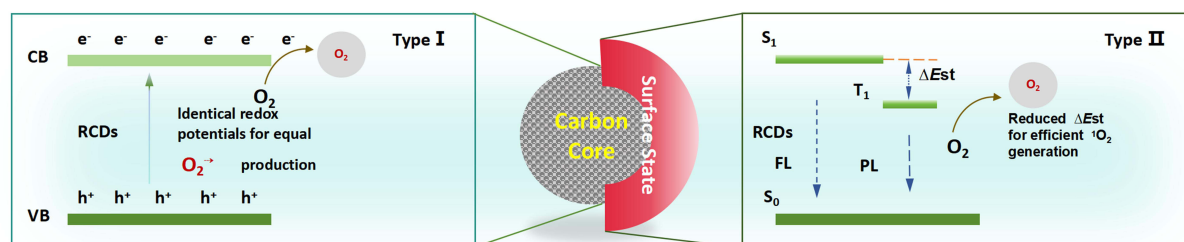


Figure 9 Description of mechanisms of CDs in PDT.



RCDs: Red carbon dots  
 PL: Photoluminescence

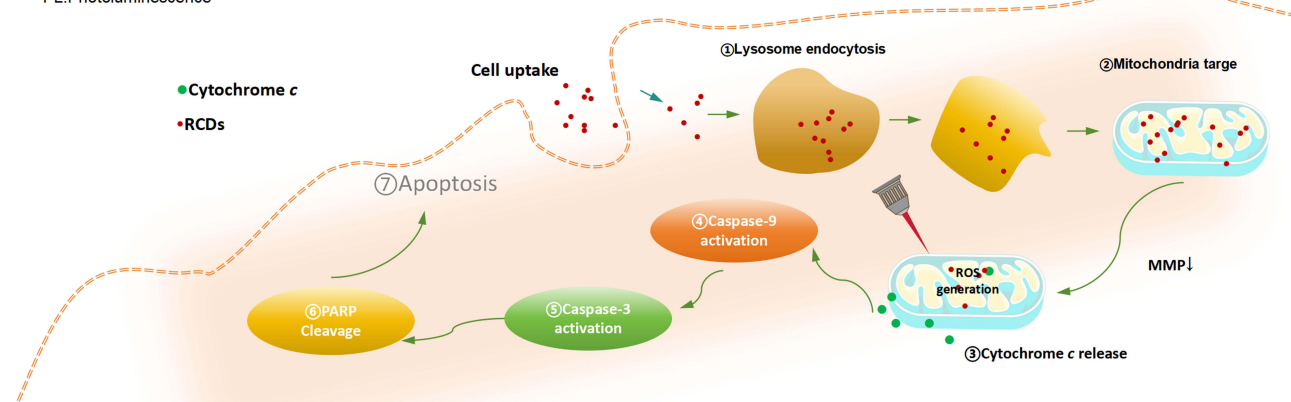


Figure 10 Schematic of RCDs as nano-PSs with tunable ROS generation.

tumor cells. The researchers found that under laser irradiation, the green fluorescence of the S-CDs treatment group was more significant than that of the 5-ALA group, indicating that the  $^1O_2$  generated by the S-CDs was traced in lysosomes and mitochondria, mediating the release of  $Ca^{2+}$  from internal storage into the cytoplasm, thereby triggering apoptosis.<sup>87</sup>

Pang and other researchers have developed a CD with bidirectional capabilities, that is, it not only has the feature of targeting but also the feature of ROS generation, which is more effective in the treatment of tumors and further improves the efficacy of PDT.<sup>88</sup> Some researchers have also enhanced the PDT effect of CDs by functionalizing them to improve targeting. The new type of CDs developed by Jia et al can overcome hypoxia and greatly enhance the therapeutic effect of PDT.<sup>89</sup> Similar studies also suggest, for instance, that the multifunctional CD nanocomposites designed by Zheng et al can significantly reduce the limitations of hypoxia on PDT in malignant tumors.<sup>90</sup> In their research work, it was confirmed through cell viability experiments that functionalized CDs can eliminate the PDT resistance induced by hypoxia, and has good growth inhibition effect on tumor sites at 1% O<sub>2</sub> concentration, showing superior ability to overcome cancer hypoxia.

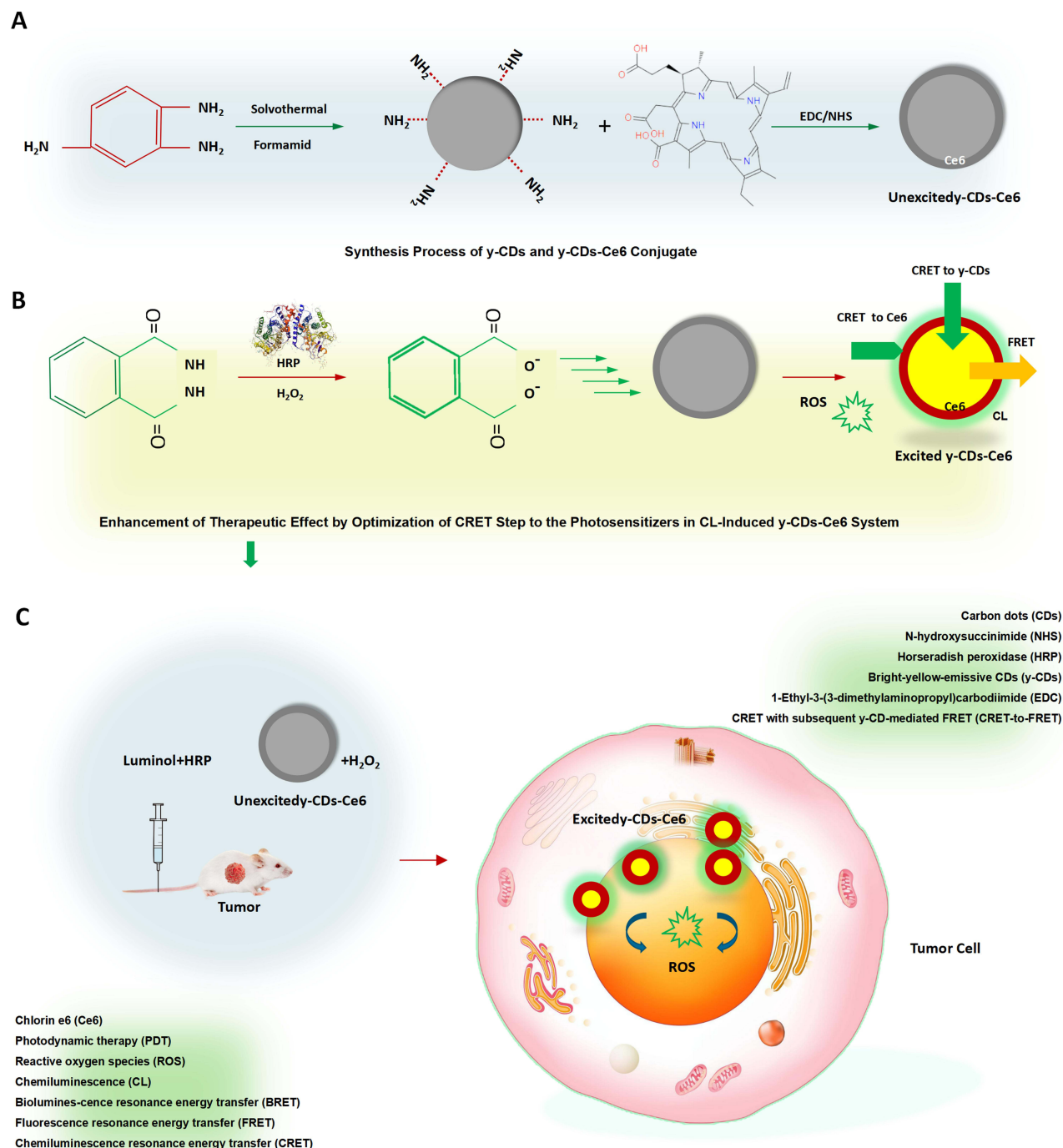
## Carbon Dots Based Nanoparticles for Photodynamic Therapy of Tumors

PDT is an activation therapy for antitumor activity. The rise of NDDS has made a tremendous advance in the domain of PDT.<sup>91–93</sup> CDs are an ideal and novel nanomaterial, considered a perfect candidate for photosensitizer delivery systems because of their various excellent features. Researchers have developed a novel self-luminescent PDT system, which aims to improve the total PDT yield with efficient absorption by optimizing the CRET step between light and photosensitization. When coupled with yellow light-emitting CDs (y-CDs), the performance of the photosensitizer is extremely enhanced, and its Soret band and Q band can be motivated directly or indirectly by CL (Figure 11), and has potential to be implemented in tumor therapy. The study showed the potential treatment effect on cancer cells, by providing a feasible method to heighten photons while reducing the toxicity of CL. This CDs-based PDT has shown superiority in overcoming the deficiency of penetrating radiation and curing deep lesions that are difficult to solve with traditional PDT.<sup>94</sup>

Overall, CDs-based NDDS has broad prospects for application in PDT therapy and has the potential for targeted GBM therapy. We hope to conduct further clinical studies in the future to benefit more patients with GBM.

## Photodynamic Therapy and Photothermal Therapy Combination Therapy

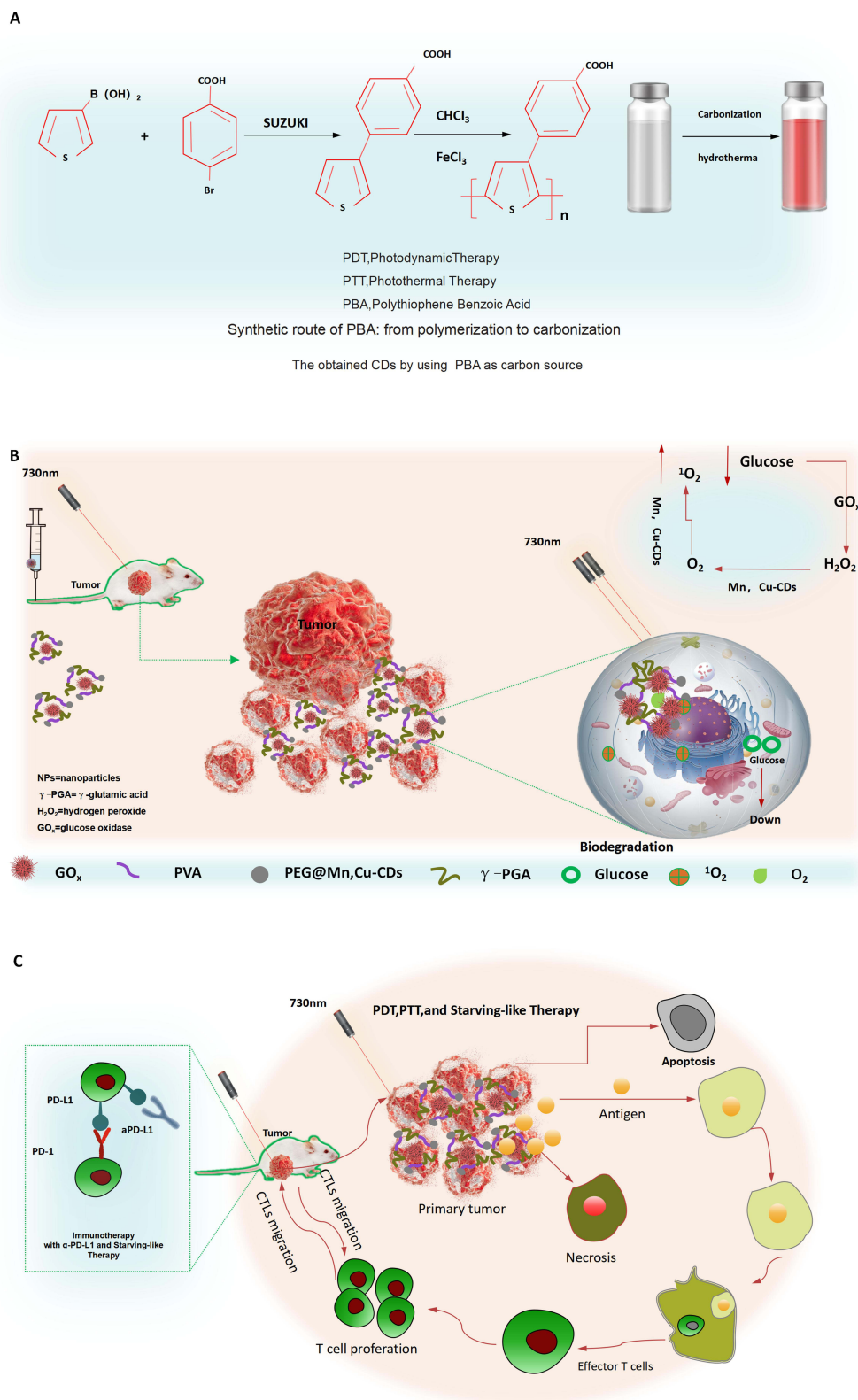
Single treatment often has certain limitations on the killing of tumors and often requires combined treatment to further increase the efficacy of treatment. Because CDs have excellent PTT and PDT characteristics, PTT and PDT treatment in a single NDDS can afford a relatively better treatment effect against tumors than either PTT or PDT alone. In general, PS acts as PDT agents in the tumor microenvironment (TME) and can induce generation of ROS under a certain amount of light, to achieve effective therapeutic purposes. However, to date, the ROS generation efficiency of PS from CD has been significantly restricted because of its poor solvability, light instability, and other factors. Accordingly, combination treatment of PDT with PTT may offer relatively excellent and unique antitumor activity. Due to increased tissue oxygen consumption and rupture of blood flow in tumor neovascularization, local anoxia of the tumor environment further interferes with and limits the curative effects of PDT. Therefore, combined therapy can overcome the problem of hypoxia and improve anticancer activity. In contrast, combination treatment could also address PS deficiencies based only on PDT or PTT. To date, researchers have continuously attempted to exploit light-triggered association treatments. For example, Ge et al developed CDs with both PTT and PDT traits using polythiophene benzoic acid as a carbon source (Figure 12A).<sup>95</sup> In addition, neoteric nanomaterials have been designed to strengthen tumor therapy through the combined action of PDT and PTT by studying the uptake of polymer-polygamma-glutamate (gamma-gamma-glutamate) (gamma-PGA) by integrating gamma-glutamyltransferase (GGT) enzymes.  $\gamma$ -PGA@GOx@Mn, a Cu-CD preparation comprise a photosensitizer and self-supplying oxygen nanoparticle obtained by glucose metabolism reacting glucose oxidase (GOx), Mn, Cu-CDs.  $\gamma$ -PGA@GOx@Mn, Cu-CDs NPs remain in a slightly acidic environment of the tumor for a prolonged time and can further target cancer cells. Under 730 nm laser irradiation, NPs also achieve excellent photothermal and photodynamic effects and could significantly alleviate tumor hypoxia through endogenous formation of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), further strengthening the curative effect. The combination treatment of PDT and PTT is effective and deserves further study to achieve tumor cure (Figure 12B and C).<sup>96</sup>



**Figure 11** Schematic of the PDT System in vivo. **(A)** Synthesis process of  $\gamma$ -CDs and  $\gamma$ -CDs-Ce6 conjugate. **(B)** Enhancement of therapeutic effect by optimization of CRET step to the photosensitizers in CL-induced  $\gamma$ -CDs-Ce6 system. **(C)** The mechanism of PDT.

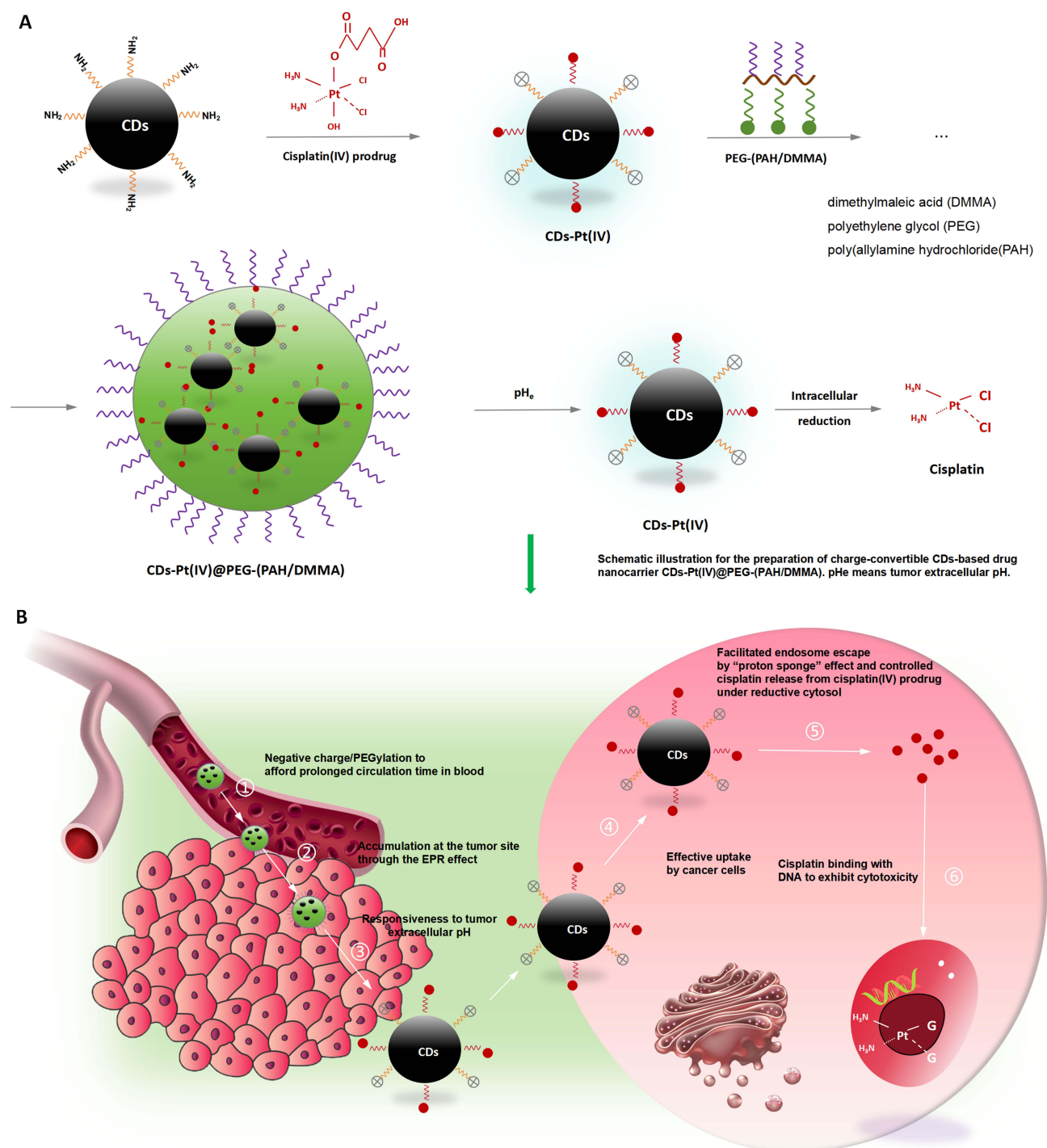
## Carbon Dots Based Drug/Gene Delivery

Chemotherapy (CT) is the most routine treatment for all kinds of malignant tumors. However, many factors, such as the drug resistance mechanism of the tumor, poor targeting of the drug and the tumor barrier, seriously limit their therapeutic effects in vivo. Thus, various NDDS have been developed to achieve enhanced targeted therapy against tumors and reduced drug resistance. In this field, CDs are also used as nanocarriers to encapsulate drugs, proteins, or cellular transmembrane peptides that target the TME through their unique surface structure to trigger targeted-release capabilities for precise drug delivery. In



**Figure 12 (A)** Synthetic route of PBA and CDs with simultaneous PTT and PDT capability by polymerization to carbonization. **(B)** Schematic illustration of starving and phototherapy mediated by  $\gamma$ -PGA@GO<sub>x</sub>@Mn, Cu-CDs NPs. **(C)** Schematic illustration of starving-like therapy, phototherapy, and immunotherapy mediated by  $\gamma$ -PGA@GO<sub>x</sub>@Mn, Cu-CDs NPs.

addition to better optical imaging and efficient drug encapsulation rates, these CD nanocarriers have shown excellent biocompatibility, safety, and low or no toxicity. The maximum drug loading of CDs is close to 96%, and there is no obvious inhibition of cell growth and inflammatory reaction. For example, Feng et al developed CDs-Pt(IV)@PEG-(PAH/DMMA), a drug nanocellular carrier with tumor extracellular microenvironment responsiveness based on preloading of the CT drug cisplatin (IV), as a bioimage-guided drug delivery system (Figure 13). This research offers a viable alternative to enhance the potential clinical application of CDs in antineoplastic protocols.<sup>97</sup>



**Figure 13** Schematic illustration for the drug delivery process of CDs-Pt(IV)@PEG-(PAH/DMMA). (A) Synthetic process of CDs-Pt(IV)@PEG-(PAH/DMMA). (B) The Drug release mechanism CDs-Pt(IV)@PEG-(PAH/DMMA).



Gene therapy is a viable potential strategy for the cure of multiple tumors but demands a secure and effective vector for delivery. The unique properties of CDs make them an efficient novel gene carrier. Liu and his research team successfully developed a high-efficient dual functional nano gene vector based on polyethylenimine-passivated CDs as transfection agents via one-step strategy technique. Their research results indicated distinct fluorescence and better solubility with low cytotoxicity (The cell survival rate is approximately over 80%) and efficient in vitro DNA transfection.<sup>98</sup>

Kim et al contrasted the mechanism of PEI-functionalized C-dots (PEI-CDs), PEI-functionalized gold colloids (PEI-AU), and plasmid DNA (pDNA) in gene delivery through DNA transfection, and the results manifested that PEI-CDs and PEI-AU achieved poor fluorescence efficiency during transfection (The transfection efficiency was almost PEI25k close to approximately  $1.0 \times 10^7$  RLU/mg protein). After the PEI-C-dots were separated from the PEI-AU, it achieved a higher concentration of pDNA and high fluorescence, which promotes gene transfer and transport.<sup>99</sup> Recently, Zhang et al have also exploited hyaluronic acid (HA)/PEI modified C-dots (HP-CDs) for tumor targeting and gene therapy. HP-CDs are easily implanted into cancer cells by endocytosis. The results suggest that HP-CDs are a potential vector for gene delivery.<sup>100</sup>

To sum up, CDs possess prominent development superiority in terms of transmission, especially for drug/gene delivery and deserve to conduct in-depth research and delve into anti-tumor applications.

## CDs-Mediated Activation of the mTOR Signaling Pathway

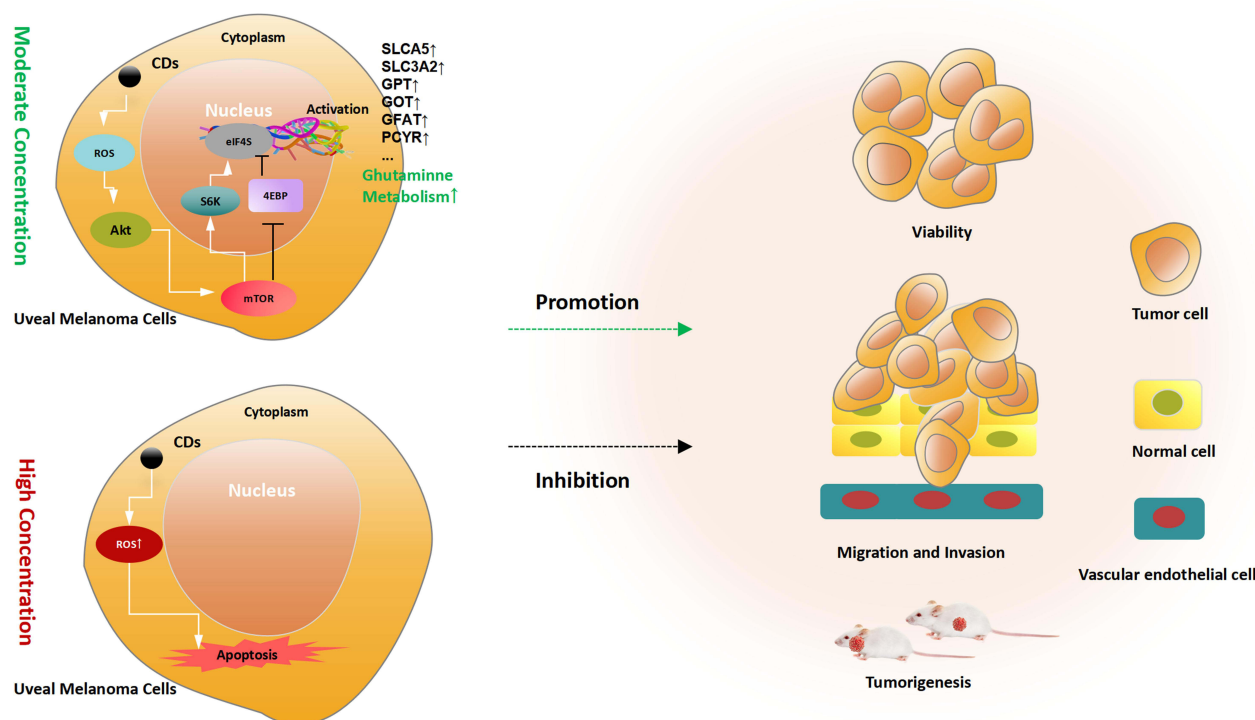
Reduced glutathione (GSH) is a strong antioxidant, and ROS can be eliminated by it. When cells are damaged and in an oxidative stress state, GSH can afford the speedy metabolic response in the first instance.<sup>101,102</sup> In view of the excellent bio-safety and compatibility of CDs, CD-based NPs have found prominent application in the monitoring and cure of malignant tumors. However, at present, the effects of CDs on tumor proliferation and cell metabolism are not fully understood, especially with regard to the regulation of tumor signaling pathways. The fundamental researches have manifested that CDs can increase ROS levels in UM cells in a dose-dependent manner. When the CDs concentration was  $<100 \mu\text{g/mL}$ , CDS-induced ROS could further increase the proliferation of UM cells and enhance cell aggressiveness. At  $200 \mu\text{g/mL}$ , UM cells underwent further apoptosis. The addition of antioxidants reversed the proteinogenic effect of CDs. A concentration of  $25\text{--}100 \mu\text{g/mL}$  CDs stimulate Akt/mTOR signaling, promote glutamine metabolism, and generate a cascade that accelerates UM cell proliferation. These data suggest that moderate subapoptotic doses of CDs facilitate tumorigenicity in UM cells. This feasibility study provides strong support for the combined effectiveness of ROS NPs in future cancer therapy (Figure 14).<sup>103</sup>

The results of the above studies provide a very useful strategy for exploring CD-mediated signaling pathways and provide new insight and reference for further treatment of tumors.

## Tumor Microenvironment-Responsive Imaging and Synergistic Tumor Treatment by CDs-Based NPs

The TME is characterized by angiogenesis, acidosis, and hypoxia, and provides a suitable environment for the growth and erosion of tumor cells, plays a crucial role in tumor deterioration, aggressive metastasis, and drug resistance, and thus, offers a breakthrough for exploring new anticancer strategies.<sup>104,105</sup>

The unique properties of the TME can provide a therapeutic target available for tumor cells.<sup>106</sup> For purpose of achieving precise the cure of tumors, the use of smart nanomaterials with therapeutic capabilities responsive to TME stimulation is currently one of the most effective methods, with visible strengths in increasing therapeutic effect and lessening side effects.<sup>107</sup> Although a more substantial study has been conducted on the design and development of TME-triggered nanotherapy platforms, it is still highly desirable to develop an easy way to manufacture such nanotherapy-borne systems with satisfactory results.<sup>108</sup> Some researchers have modified CDs (CDs-Ce6) and  $\text{Cu}^{2+}$  by assembling a photosensitizer (chlorine e6, Ce6) to prepare TME stimulus-responsive NDDS, which can not only be used for fluorescence imaging, but also can be applied for collaborative tumor treatment. Due to the assembly of CDs-Ce6, the obtained nanocomponents (called Cu/CC, NPs) reveal quenched FL and photosensitivity. FL imaging and PDT function are effectively restored after penetration of the tumor under TME stimulation. The introduction of  $\text{Cu}^{2+}$  not only provides an attached CDT impact by reacting with  $\text{H}_2\text{O}_2$  but also eliminates GSH in tumors through REDOX reactions; therefore,



**Figure 14** Schematic of the opposing CDs-concentration-dependent effects on tumor cell progression and metastasis.

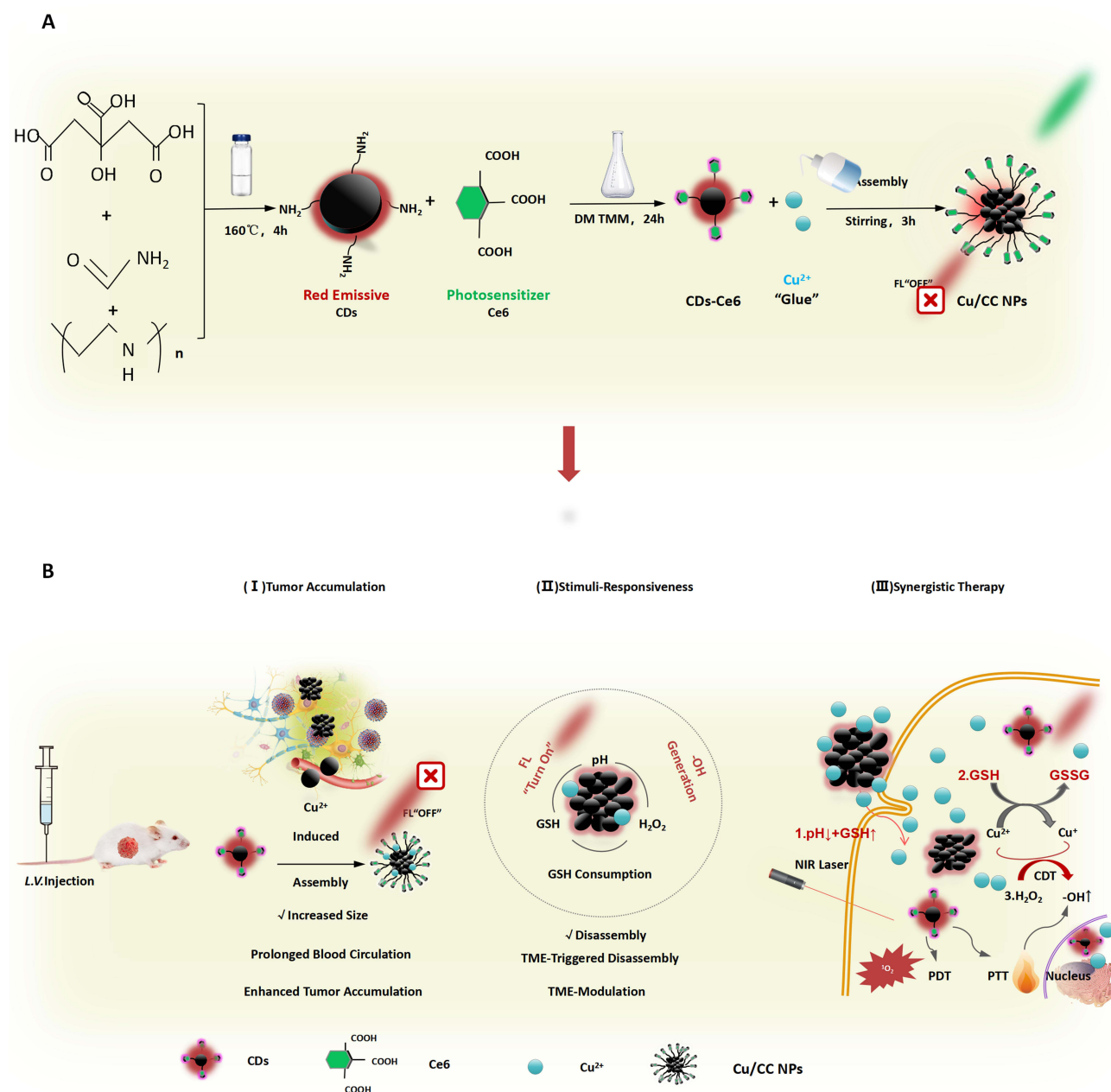
oxidative stress can be improved and the effect of ROS treatment can be enhanced. Cu/CC NPs can be used as a triad of FL-image-guided anti-tumor properties by PTT, PDT, and CDT (Figure 15).<sup>109</sup>

In summary, using CDs, we can design a nanoplatform with remarkable characteristics of TME stimulating response fluorescence imaging and PTT, PDT, and heat-enhanced CDT synergistic therapy, which can improve the therapeutic efficiency related to ROS and take advantage of the virtues of TME to effectively heighten curative effects and reduction of toxic and side effects.

## CDs Penetrate the BBB

One of the largest impediments to the efficient remedy of gliomas is that most drugs cannot smoothly cross the blood-brain barrier (BBB). The unique microvascular system is a natural block that strictly limits the flow of molecules into and out of brain tissue. Although, tight connections between endothelial cells allow certain substances to cross the BBB. According to statistics, approximately 98% of small molecules and almost 100% of macromolecules cannot easily pass through the BBB, which strictly limits the effective concentration of glioma treatment drugs, such as temozolomide (TMZ).<sup>110</sup> Nevertheless, through the ingenious encapsulation or modification of NDDS, researchers have conducted experiments to verify that both surface-modified or functionalized CDs and naked CDs can traverse the BBB. Adopting a zebrafish experiment, Li et al and Vallejo et al believed that CDs synthesized with carbon powder could not traverse the BBB by traditional synthesis methods, such as top-down methods. However, when modified with the iron transport protein, these CDs easily crossed the BBB.<sup>19,111</sup>

The presence of highly expressed transferrin receptors (TfRs) in brain endothelial cells makes them ideal targets for transferrin-binding CDs and other NDDSs to cross the BBB through receptor-mediated endocytosis. Although TfRs are generally used to promote BBB traversing, other receptors present in the BBB can also be used for delivery. These include angioendotelin-2, which can penetrate the BBB and can serve to transport cargo to brain tissue or cells. Liu et al also confirmed that endothelin-2-modified CDs can fully penetrate the BBB of mouse C6 gliomas.<sup>112</sup> Similarly, CDs can also be synthesized



**Figure 15** Schematic of (A) the synthesis process of Cu/CC nanoassemblies and (B) their features for enhancing tumor accumulation, TME stimuli-responses and synergistic therapy.

using the glucose transporter GLUT1 or the L-amino acid transporter 1 (LAT1), which are expressed at high levels throughout the BBB. Kirbas Cilinger et al proposed that fluorescein-coupled CDs prepared by glucose easily cross the BBB.<sup>113</sup>

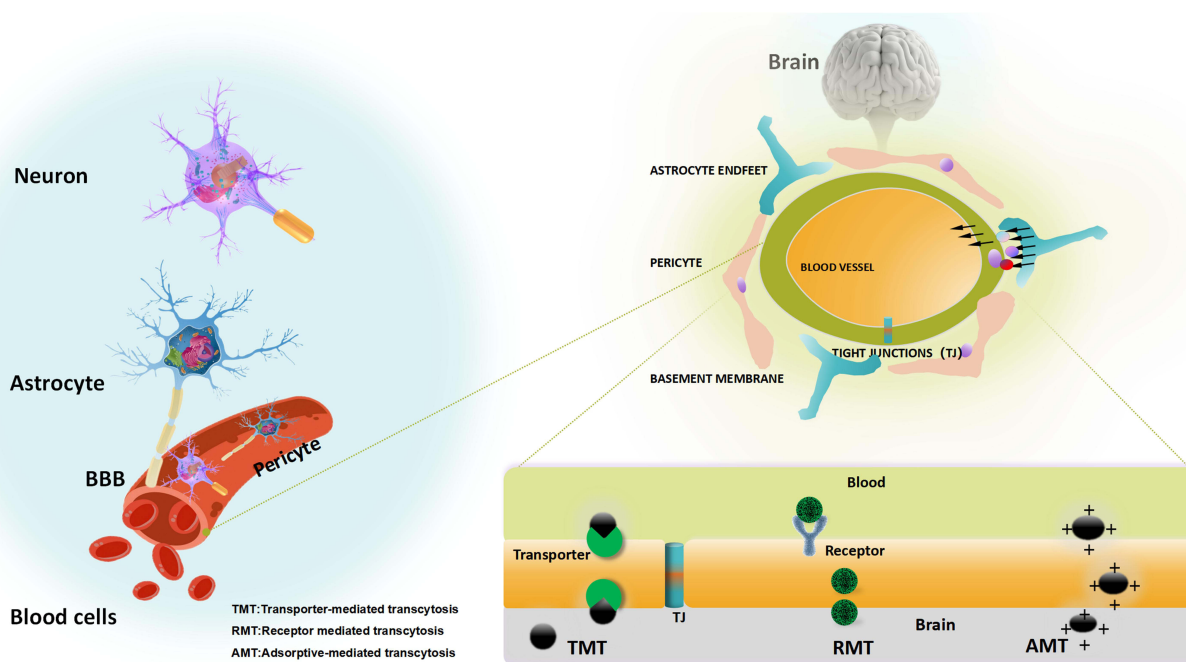
Initially, CDs could be uniformly dispersed and permeated in all cells. Research has found that CDs can not only be taken up and accumulated in normal cells, but also be taken up and accumulated in malignant tumor cells, which will further confirm that CDs have good dispersibility and penetrability.<sup>114</sup> However, the enhanced permeability and retention (EPR) effect has led miscellaneous researches to observe characteristic of the distinctive accumulation of CDs in cancer cells. The research of Su et al manifested that CDs firstly accumulated at the tumor microenvironment and were efficiently eliminated by circulatory system or metabolic system (for example, the kidney organ).<sup>115</sup> Their research found that Hf-CDs have advantages such as the ability to target tumor accumulation preferentially. Meanwhile, it was also found that the reason why Hf-CDs can achieve rapid imaging is that CDs are highly likely to accumulate at the

tumor site. To take advantage of the targeted imaging of CDs, researchers improved the cell uptake function enhanced by magnetic field to promote unique accumulation. Their research indicates that CDs NPs can target tumors by EPR.<sup>116</sup> In conclusion, the effect regulation of BBB penetrability, EPR effect, endocytosis and excellent penetration power jointly contribute to the high targeting ability of CDs for brain tumors.

The penetration ability of CPDs was evaluated by co-establishing BBB model using human endothelial and C6 cells. The results suggested that CPDs had a good capacity to cross the BBB. Therefore, it can be used for the diagnosis and treatment of brain cancer, such as GBM. In vivo and in vitro imaging of rats with orthotopic glioma indicated that the targeted potential of CPDs for brain tumors was further confirmed. And it is suggested that CPDs may target gliomas rather than abnormal brain tissues. Furthermore, CPDs can clearly depict the boundaries of brain tumors, demonstrating the feasibility of CPDs for the visualization and localization of brain tumor surgeries.<sup>112,117</sup> Similarly, Mintz et al used a zebrafish model to demonstrate that tryptophan cd can also easily cross the blood–brain barrier. Another way for CD to cross the blood–brain barrier involves adsorpt-mediated cell transport, which relies on the electrostatic interaction between brain capillary endothelial cells and CD. The common methods for delivering cargo through BBB are displayed in Figure 16.

Through proper modification, functionalization, or covalent coupling, CDs can transport clinical chemotherapy drugs break through the BBB, providing new hope for the cure of various malignant tumors in the future. However, additional trials are needed to verify whether CDs can pierce through the BBTB, and more trials are needed to further probe and investigate the mechanism of penetration.

In fact, certain properties of NPs have been revealed to allow drugs to enter the central nervous system by conquering the BBB.<sup>118</sup> Compared with metal-based NPs, CDs have lower cytotoxicity and superior bio-compatibility, so scholars have focused on it. In addition, the synthesis method of CDs is easy and the surface to volume ratio is high, which makes it possess a high drug encapsulation and loading rate. Due to its superior PL properties, the biological distribution of CDs can be monitored in vitro and in vivo studies. In addition, some CDs may be capable of piercing the BBB due to a number of beneficial surface properties, including low charge and amphiphilicity. In vitro and in vivo models have been established to verify whether CD and CDs covalent conjugate can cross the BBB. Lu et al prepared nitrogen-doped CDs (N-CDs) in a one-pot hydrothermal process and verified their competence to penetrate the BBB using an in vitro test model composed of endothelial cells and astrocytes, with satisfactory results.<sup>119</sup> At the same time, the study also demonstrated that N-CDs are capable of crossing the BBB in the form of concentration and time dependence, which



**Figure 16** Schematic of the BBB and mechanisms by which CDs may cross.

can put down to their small particle diameter ratio. In addition, the cation PEI on the surface of N-CDs also facilitates the infiltration of BBB.<sup>119,120</sup>

Table 4 provides research reports of functionalized CDs penetrating the BBB.

## Active Targeting of Carbon Dots Based Nanoparticles

Brain tumors range from benign to malignant. Two tumors that receive a similar pathological diagnosis could differ enormously in their susceptibility to the treatment. Furthermore, especially in malignant tumors such as GBM, individual cell populations within the same tumor tissue can also present differences in the expression of gene, various proteins, and also may regulate a variety of signaling pathways, and may present different sensitivities to certain therapies. Effective treatments should consider the intertumor and intratumor heterogeneity, which highlights the importance of targeted specific tumor tissue interventions. To date, different types of NDDS used in diverse trials have relied on reinforced EPR. This mechanism depends on the passive accumulation of NPs within the tumor in that reduced vascular leakage and lymphatic drainage, which is a significant reason in the development of NDDS.<sup>126,127</sup> However, the trial data showed that only a small quantity of the drug can accumulate in tumor tissue or cells.<sup>128</sup> In the process of uptake of cellular CDs, two main uptake mechanisms are involved. The first is a passive pathway, which refers to non-receptor-mediated uptake of CDs through diffusion or endocytosis, whereas the other is an active pathway, which refers to transporter- and receptor-ligand-mediated uptake of CDS in cells.<sup>121,129,130</sup> CDs can be covalently coupled to ligands and drug cargoes by a link-agent or electrostatic coupling, resulting in the release of drugs in a particular environment through a specific pH microenvironment or through reductase-dependent bonds. For example, disulfide bonds. To efficiently deliver drugs to specific targets, the enzyme and cascade of signaling pathways that target the tumor, the TME, and the cell must be considered. Understanding the expression of glioma subtypes will especially help researchers design CD-based drug delivery targets. Approaches to build up tumor cell selectivity mainly contain the use of membrane receptors, transporters, regulation of signaling pathways, and alteration of tumor cell metabolism and migration. Thus, tumor cells exhibit strong glycolysis and amino acid metabolism activity. By exploiting nanospecific biomorphology, CDs can generate targeted glycolysis. Furthermore, due to the presence of the glucose transporter GLUT-1 and the AA transporter LAT1 on the BBB, these CDs can penetrate the BBB for imaging and drug delivery, thus achieving effective treatment of glioma. Studies of T cells for the cure of cell surface antigens in aggressive brain tumors have identified several promising drugs targeting NP-mediated NDDS.<sup>131</sup> The most common targeted antigens are shown in Table 5. Most antigen-targeted functionalized NDDS have been shown to have anticancer effects and may also be used for NP-mediated drug delivery. Another option for CDs-mediated brain tumor cure is to target the TME. Using bevacizumab to target blood vessel growth, VEGF inhibitors have been shown to prolong the life of patients with GBM and have achieved a cure for recurrent GBM.<sup>132</sup> In the early years, scholars confirmed the antiangiogenic effects of anti-VEGF aptamer modification of CDs in animal experiments.<sup>133</sup>

**Table 4** Research Reports of Functionalized CDs Penetrating the BBB

Type	Size	Surface Conjugated	BBB Model	Refs
Nitrogen-doped-CDs	2.6nm	Amine (-NH <sub>2</sub> ), Carboxyl (-COOH)	Transwell	[119]
Yellow-emissive-CDs	3.4nm	Amine (-NH <sub>2</sub> ), Carboxyl (-COOH)	Zebrafish	[121]
EDA-T-CDs	6.2nm	Amine (-NH <sub>2</sub> )	Zebrafish	[122]
Urea-T-CDs	4.1nm	Amine (-NH <sub>2</sub> ), Carboxyl (-COOH)	Zebrafish	[122]
Saccharide-based CDs	4.0nm	Carboxyl (-COOH), Hydroxyl (-OH), Carboxylate	Zebrafish/Rat	[123]
Protein-based CDs	8.0nm	Amine (-NH <sub>2</sub> )	Mice	[124]
Mn-doped CDs	4.0nm	Amine (-NH <sub>2</sub> ), Carboxyl (-COOH), Hydroxyl (-OH)	Mice	[125]
IL-6-CDs	3.3nm	Amine (-NH <sub>2</sub> )	Mice	[112]
CDs	5.7nm	Amine (-NH <sub>2</sub> )	Rat	[38]



**Table 5** Potential Antigens and Targeted Ligands for CD-Mediated Drug Delivery to GBM

Targeted Molecule	Role	Ligand	Targeting Ligand(s)	Ref.
IL13R $\alpha$ 2	Receptor	IL13	Pep-I (peptide)	[134]
EGFR	Receptor	EGF and neuregulin	GEI I Peptide	[135]
GD2	Ganglioside	Not identified	Anti-GD2 antibody	[136]

**Notes:** GEI I (YHWYGYTPQNVI, Mw (Molecular weight) 1540 g/mol, IP 7.67) is a dodecapeptide whose excellent EGFR affinity was demonstrated. GD2: Disialoganglioside 2 is a highly glycosylated sphingolipid which has been shown to be highly expressed in high-grade gliomas.

**Abbreviations:** EGFR, epidermal growth factor receptor; IL13, interleukin.

Targeting immune cells is also currently considered a new treatment option for GBM. At the same time, integrin families that target transmembrane proteins are also a potential target for targeted drug delivery systems against GBM. A pH-dependent cisplatin drug has been developed that releases integrins to target CDs and shows significant tumor cell apoptosis, and even complete decomposition or death in a lower pH environment, thus targeting numerous levels of the TME.<sup>137</sup>

CDs have the potential for broad application in active targeting strategies, but the specific potential targeting mechanism and regulation of signaling pathways are not currently very clear, which is also a basic research issue that we need to explore and elucidate in the future.

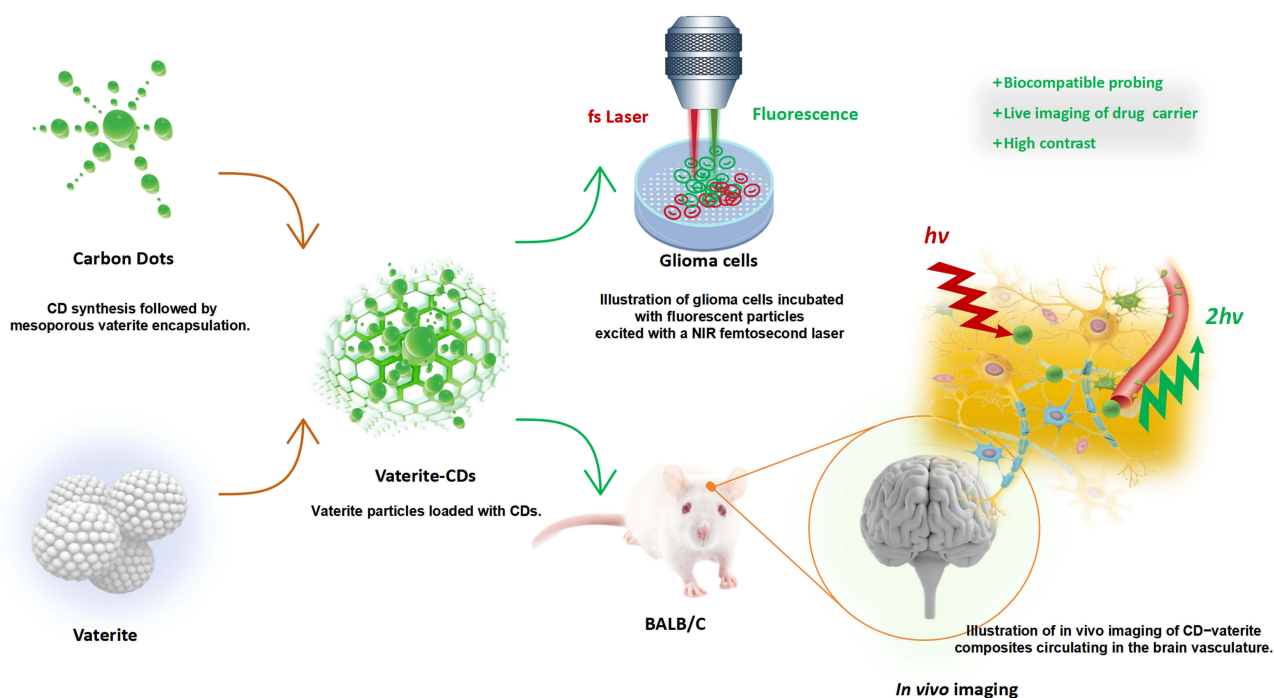
## In-Brain Multiphoton Imaging

Biocompatible fluorescent agents are a key factor in real-time in vivo imaging. The optical features of CDs support their feasibility for fluorescence imaging of the brain microstructure. Mesoporous vaterite NPs have been encapsulated with CDs to investigate the potential of a biocompatible image and the imaging efficacy of CD-vaterite compounds absorbed by different cells has been demonstrated. The CD-vaterite compound injected into mice allowed the hemodynamics within brain blood vessels to be monitored through cranial windows. These experimental results manifest that the platform possesses the capacity to achieve high-resolution biocompatibility imaging with both sensing and drug delivery capabilities (Figure 17). Finally, the interaction between CD-vaterite composites with MDM-DA-231 and C6 glioma cell lines using single-photon and two-photon confocal microscopy was evaluated. Injections of the CD-vaterite complex allowed visualization for the first time of the brain vessels of mice. In this way, particles in the blood can be tracked, accelerating the tracing of blood vessels and the BBB. Furthermore, with further improvement, the method can investigate drug–cell interactions in real time.<sup>138</sup>

In summary, CDs and vaterite coupling have strong potential as a multifunctional tool for glioma research and treatment, and can distinguish tumor tissue from normal brain tissue through intraoperative fluorescence agent tracking, and can further evaluate the heterogeneity of the neovasculature in tumor tissue. However, further research is needed before entering preliminary clinical trials.

## Carbon Dots Based Nanoparticles for Treatment and Diagnostics of Glioblastoma

GBM is the most difficult tumor to treat and eradicate. In addition to PDT and PTT, SDT is a novel therapeutic measure, whose principle is to activate an acoustic sensitizer through low-intensity ultrasound to destroy the tumor. A new type of acoustic sensitizer was developed and delved adopting Cu-doped carbon dots (Cu-CDs) for the sonodynamic therapy of GBM. Cu-CDs were skillfully synthesized adopting one-step hydrothermal method using IR775 (I) and copper acetylacetonate. To assess the capability of Cu-CD, the therapeutic effects of Cu-CD were tested on glioma by establishing U87 an in situ tumor. Surprisingly, Cu-CDs crossed the BBB and enter glioma tissue, not only in that their small controllable particle size but also the negative charge of Cu-CDs helped to precisely permeate the BBB and enter brain tumors. During the whole treatment period, no death events were observed in Cu-CD+US group, indicating that SDT has a powerful anti-tumor effect. The weight of the experimental mice did not change significantly, confirming the bio-safety of SDT in the cure of brain tumors in animal models. With such a pronounced therapeutic effect, the researchers



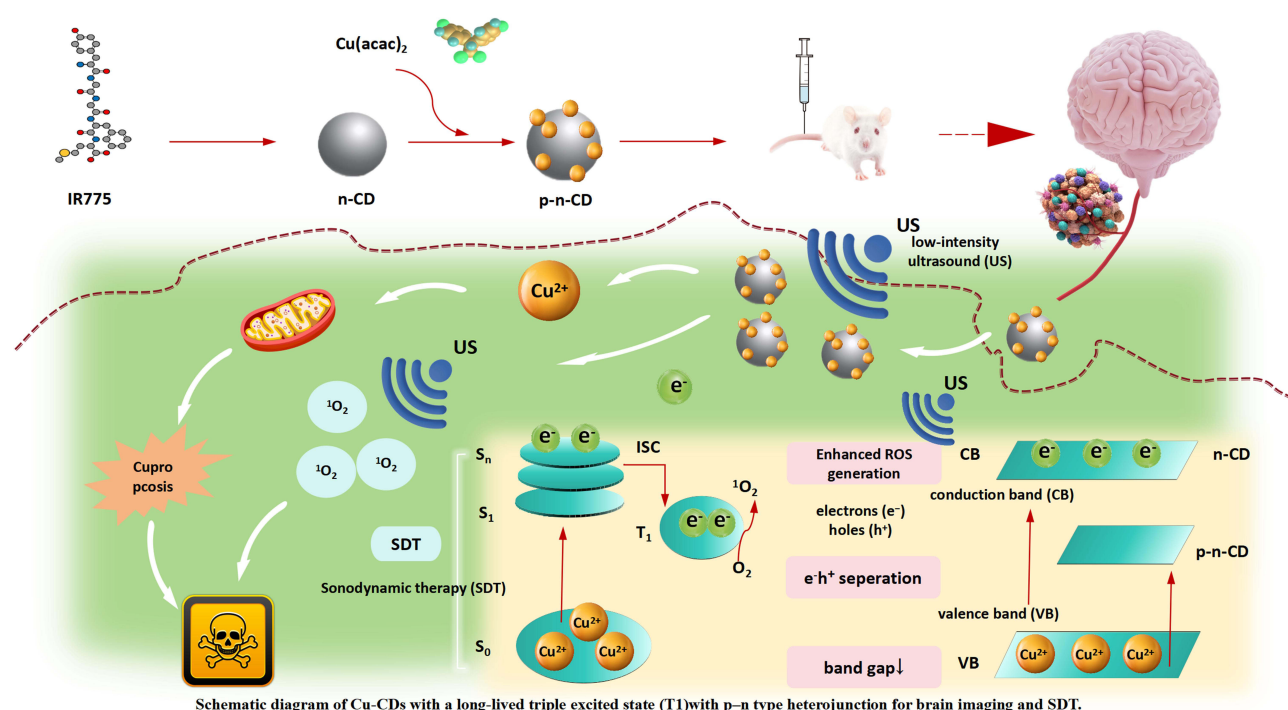
**Figure 17** Experimental concept.

speculated that Cu-CD+US may initiate Cu-induced apoptosis, known as cuproptosis, in tumor cells during therapy, hence enhancing the total therapeutic effect of a synergistic anti-tumor way that combines SDT with the coordinated process of Cu-induced cell death. In addition, immunofluorescence analysis showed that the Cu-CD+US group achieved a considerable tumor inhibiting effect, and this phenomenon ascribe copper doping, which helps to enhance the sonodynamic therapy of Cu-CDs and the powerful biological influence of copper precipitation, further triggering tumor cell apoptosis (Figure 18).<sup>139</sup>

The marked BBB permeability and potent anti-tumor effect of Cu-CDs highlight their potential capacity in the targeted therapy of GBM. In the future, multi-modal schemes can be attempted to conquer GBM, such as PDT+PTT+SDT. The progress of CDs nanotechnology not only brings new hope for cancer treatment but also provides new ideas and breakthroughs for future basic and clinical research.

Early diagnosis of GBM is crucial, and early treatment is also a feasible method to heighten the prognosis of patients. A strategic approach involves the use of antibodies (Abs) to monitor gliofibrillary protein (GFAP) in samples. GFAP is specific to the brain tissue and does not exist in normal peripheral blood. Therefore, anti-GFAP antibodies can be used for the early diagnosis of GBM and provide some indications for early treatment. Currently, researchers have used CD-based fluorescent antibody nanoprobe for the early diagnosis of GBM. Proteins and antibodies labeled with fluorescent CDs produce a robust, light-stable diagnostic probe suitable for clinical diagnosis. The scheme relies on the coupling of dibenzocyclooctyl (DBCO)-functionalized CD with azide protein and promotes the linking chemical reaction of acetylene-azide cycloaddition (SPAAC) by binding amide coupling and strain. The new antibody CD conjugate developed by this strategy can be used for the early diagnosis of patients with GBM by experimental verification (Figure 19).<sup>140</sup> The diagnostic value of CDs is compared with existing MRI (Table 6).

CD-based NDDS is a key component in the treatment of GBM, and if it is diagnosed early, it may further improve the prognosis of the patient and improve the quality of life of patients. The researches manifest that CDs can be used not only for the multi-synergistic treatment of GBM, but also for the early diagnosis of GBM via proper identification. Given the greater confidence in CD materials, one day CDs may serve clinical patients and improve their survival.



**Figure 18** Schematic diagram of Cu-CDs with a long-lived triple excited state (T1) with p-n type heterojunction for brain imaging and SDT.

## Summary of Drug Loading Rate of CDs

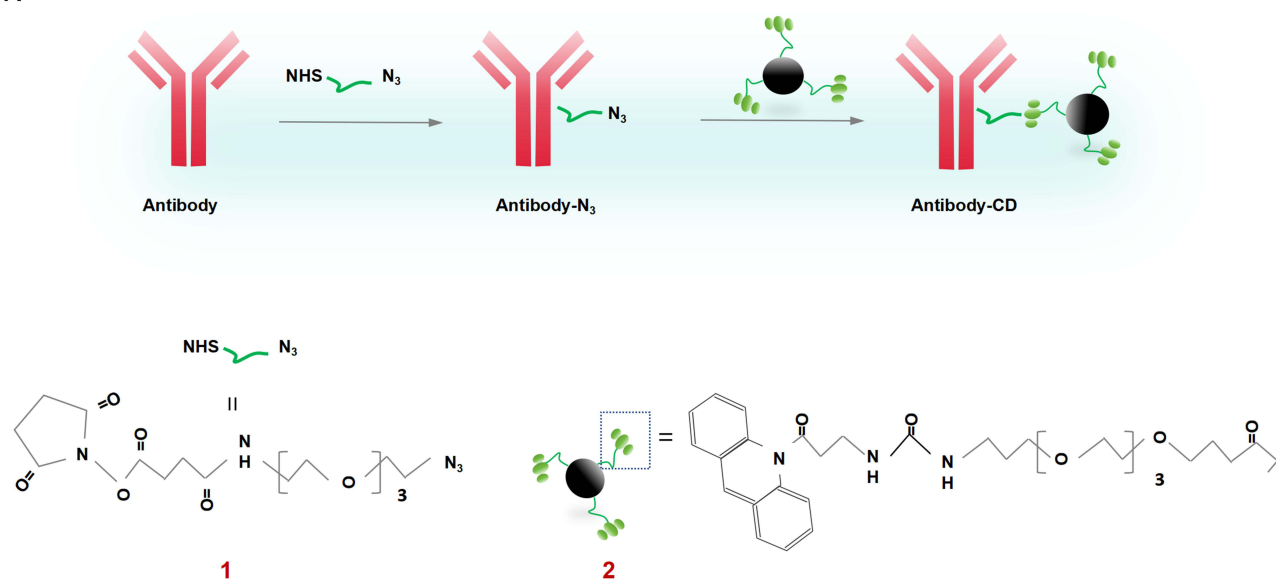
The drug loading rate of nanocarriers is crucial to the therapeutic effect, and we have summarized it as shown in Table 7 in order to provide useful information.

## Challenges and Opportunities of CDs-Based NPs Against GBM

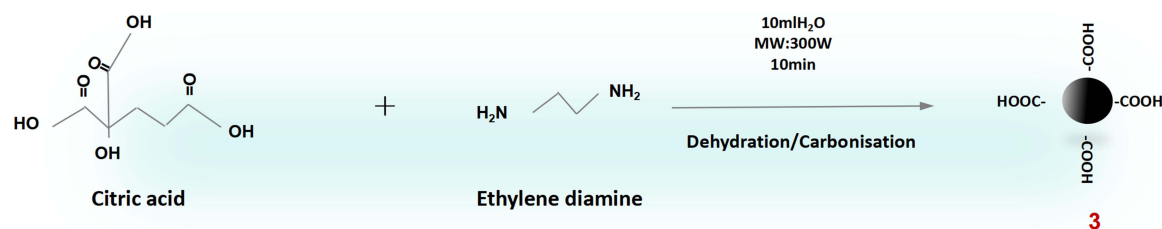
Currently, CDs are continually served as sensors, probes, drug/gene carrier and imaging devices in every field.<sup>158,159</sup> Bio-modification of CDs is also broadly used for therapy of malignant diseases, such as brain cancer, especially GBM.<sup>160</sup> However, bio-modification of CDs could make some cells delivery infeasible because of the toxicity of the raw materials used to synthesize CDs.<sup>161</sup> The mechanism of CDs metabolism and body circulation are not well understood, which induce toxicity in the animal or cell model.<sup>162</sup> Some vital and critical limitations impeding its further utilization in clinical medicine field include toxic effect, bio-compatibility, side effect, bio-availability, immune inflammatory response and biodegradability and so on.<sup>163,164</sup> The synthesis of nontoxic CDs such as bio-waste-based CDs and so on may solve above issues, especially toxic reaction.<sup>165,166</sup> Recently, the broader focus in adopting natural resources in CDs synthesis utilizing hydrothermal carbonization (HTC) method demands a minimal experimental equipment.<sup>167–169</sup> Furthermore, the approval of the regulation of CDs in the published academic papers is relatively low. At least, it has not been clinically approved and accepted yet, and needed to make unremitting efforts to achieve by every researcher and explorer.

According to the plasticity and modification of nanomaterials, the functionalization and covalent attachment of the surface could modify the physical characteristics, which could have extremely influence on their photoluminescence characteristics. The *in vitro* results indicated the strong anti-tumor features, showing them as potential replacements for imaging and medical applications because of the impacts of these nano-CDs purposes. CDs-based NPs have undergone three technological change. The first time is that they experience a relatively short circulation and accumulate in the spleen. This is because they lack a certain specificity and are instead more easily swallowed by the immune system. The second time is that CDs-based NPs are protected from the immune system, possess better solubility, and are less easy to gather when modified with polymer chains, such as PEG. However, the EPR effect could trigger these NPs to stay in particular position of the tumor microenvironment, such as tumor imaging.<sup>170</sup> Due to a leaky, increased vascular permeability vascular system and the deficiency of lymphatic drainage. NPs can concentrate a specific target or tissue

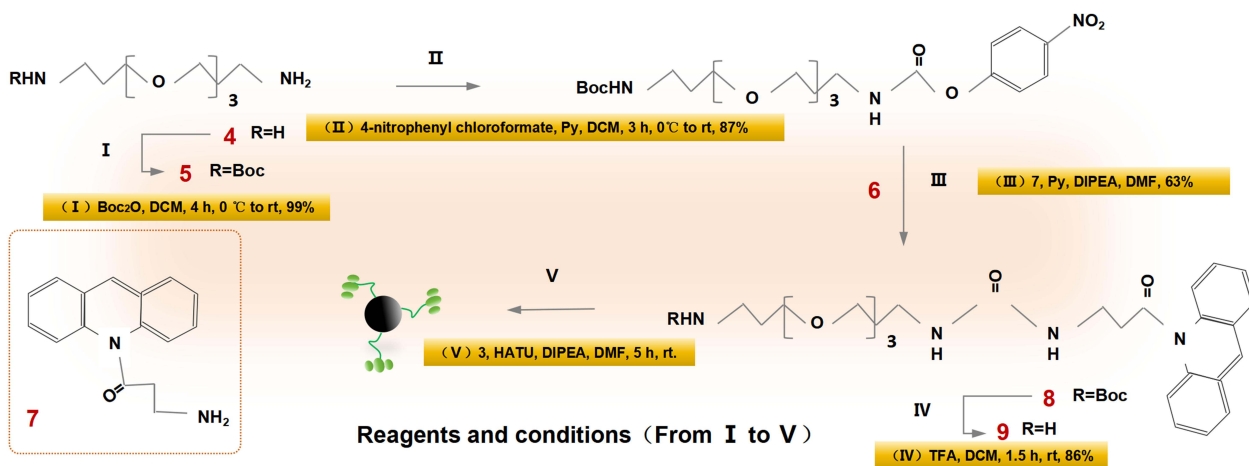
A



B



Synthetic approach for the synthesis of acidic coated CDs 3.



**Figure 19** General Antibody-CD conjugation strategy. (A) Synthetic process of antibody-CD. (B) Reagents and conditions (From I to V).

of tumor. Regrettably, this influence is multifactorial hinging on tumor characteristics, the patients, and the early stage or later stage of tumor. Third-time NPs were further modified with all kinds of conjugates, for instance, proteins, peptides, DNA or RNA and gene and so on. However, these adjustments could trigger fluorescence quenching, and thereby require to be strictly evaluated.

**Table 6** Differences Between CDs Imaging and MRI

Type	Principle	Application	Advantages	Disadvantages	Refs
CDs	CDs is a kind of zero-dimensional photoluminescent nanomaterial with particle size less than 10 nm, which has the characteristics of adjustable fluorescence emission and excitation wavelength, good light stability, water solubility and biocompatibility, and low toxicity. CDs performs imaging by absorbing and emitting photons and is suitable for fluorescence imaging in living organisms.	CDs imaging is mainly used for biological imaging, especially fluorescence imaging in organisms. Due to its good biocompatibility and low toxicity, CDs performs well in fluorescence imaging of cells and animals in vivo, suitable for staining and tracking individual organelles inside cells. At present, it is mainly used in basic research and pre-clinical trials, and is in the exploration and research stage.	High sensitivity, good biocompatibility and low toxicity, suitable for real-time monitoring in living cells and animals.	Tissue penetration is weak and imaging effectiveness is limited for deeper tissues or larger organisms.	[141]
MRI	MRI uses the principle of nuclear magnetic resonance to create an image of the internal structure of an object by applying radio frequency pulses and detecting the energy signal released by hydrogen atoms. MRI uses gradient magnetic fields and radiofrequency waves to cause hydrogen atoms in the body to resonate, and constructs images by receiving these energy signals.	MRI is widely used in the detection and early diagnosis of various diseases, especially in the imaging of the nervous system, skeletal system and soft tissue. MRI can provide high-resolution three-dimensional images, which is suitable for the diagnosis of tumors, trauma, vascular diseases, etc. It is mainly used in clinic.	High spatial resolution, capable of providing detailed three-dimensional images, suitable for imaging complex structures.	The imaging time is longer, the device costs more, and it needs to be used with caution in certain populations, such as pregnant women and children.	[142]

**Table 7** Summary of Drug Loading Rate of CDs

Type	Size	Surface	Drug	DLR (wt%)	Model	Refs
DOX-CDs	N/A	Physisorbed through interactions such as $\pi$ - $\pi$ stacking, hydrophobic and van der Waals interactions	DOX	6.0	A549	[143]
CA-CD	220 $\pm$ 25.99nm	Hydrogen bonding	b-TC	77	N/A	[144]
CDs-Oxa	2.71 $\pm$ 0.43nm	Condensation reaction between the amino groups and the carboxyl group	Oxa(IV)-COOH	4.2	L929, HepG2	[145]
CDs-Pt(IV)@PEG	125nm	Intriguing charge conversion to a cationic polymer	Pt(IV)	6.7	A2780	[146]
CDsRGD-Pt(IV)-PEG	31nm	Intriguing charge conversion to a cationic polymer	Pt(IV)	4.1	MDA-MB-231 MCF-7 cells	[147]

(Continued)



**Table 7** (Continued).

Type	Size	Surface	Drug	DLR (wt%)	Model	Refs
PNHCDS-DOX	N/A	Interactions such as electrostatic attraction, $\pi$ - $\pi$ stacking, van der Waals force, and hydrophobic interaction	DOX	35.43	HepG2, SiHa MCF-7	[137]
CD-DOX conjugates	N/A	Amines bind with the carboxylic acid via electrostatic interactions or hydrogen bonding.	DOX	N/A	HepG2 cells HL-7702 cells	[148]
P-CDs/HA-Dox	15–30nm	Electrostatic self-assembly	DOX	6.3	HeLa NIH-3T3	[149]
IL-OCDs/Cur	N/A	Hydrophobic interaction	Cur	69.2	HeLa	[150]
DOX@ACD	131±3.7nm	Amphiphilic interaction	DOX	14.2±0.003	A549	[151]
FA-Gd@CQDs/ DOX	N/A	$\pi$ - $\pi$ stacking and hydrophobic interactions	DOX	74.5±3.96	HeLa, HepG2, and HeLung cell	[152]
pCBMA (CD-D/DOX)	183 ± 27nm	Electrostatic interactions and $\pi$ - $\pi$ stacking	DOX HCl	96.9	4T1 and HepG2 cells	[153]
CDs-epi	2.6nm	Conjugated	Epirubicin	N/A	SJGBM2 CHLA200 CHLA266 U87	[154]
p(CAT2-CD-BA1)	3.79nm	Noninvasive adsorption	DOX	84.28	HeLa	[155]
CD-PEI-DOX	222.5±20.1nm	Electrostatic interactions	DOX	35.88	L02, MHCC-97L, Hep3B	[155]
DS-NA	7235±2.9nm	Hydrophobicity interaction	DOX	23.5	MDA-MB-435S, 4T1	[156]
APCDs@Fe/ DOX-LOS	106±1.5nm	$\pi$ - $\pi$ stacking interaction with large p-conjugated structure of APCDs	DOX	30.3±1.3	4T1 tumorbearing mice	[157]

**Abbreviation:** DLR, drug loading rate.

NIR emission of CDs are of extraordinary interest. In fact, the less near-infrared light is absorbed, the deeper it penetrates the tissue, up to a depth of about a few centimeters. However, due to reduced absorption coefficients of scalp, subcutaneous adipose tissue and skull, as well as oxygenated and hypoxic blood, tissue self-fluorescence is significantly reduced in the near-infrared window, especially between 650 and 950nm. Therefore, NIR CDs are attractive for biological imaging, especially for tumor imaging during surgical removal of GBM.<sup>170</sup> At present, researchers are actively exploring and studying.

In addition, one of the biggest concerns for researchers is security, especially in medical applications. First of all, it is necessary to go through large-scale basic tests to verify the toxicity of CDs, and how to reduce the potential toxicity of CDs by physical or chemical modification; Secondly, after modification, CDs-based NPs need to be evaluated again whether it has life-threatening toxicity, whether it has inevitable side effects, even if it has certain side effects, once the toxic side effects occur, how can we use other drugs to rescue or combat? This is also a key issue that we cannot avoid; Similarly, ethical review, inspection by quality inspection department, approval by health department, and various problems in the production process all require strict control by the administrative department, and no errors are allowed. Finally, entering

the clinical stage, it is more necessary to recruit more patients to participate in the evaluation of the safety of CDs-based nanodrug delivery system, so that it is possible to truly enter the clinical treatment stage. For the above problems, we need to work hard to conquer and verify step by step. However, we firmly believe that the future of CDs must be bright.

## Conclusions and Future Perspectives

GBM remains a malignant tumor that cannot be completely conquered in the world and with high morbidity and mortality rates worldwide that currently can not be completely conquered. Recently, the introduction of NDDS, as a novel treatment method, has been favored by researchers, especially with regard to CDs because of their strengths of cheap cost, high repeatability, better bio-compatibility, low toxicity, high-definition imaging, and powerful modification of tumor-specific molecular targets. This area of continues to be a research hot spot and is garnering increasing interest. The excellent characteristics of CDs make it a suitable treatment strategy for GBM, especially when compared with other NDDS, for instance, exosomes, liposomes, polydopamine, and gold NPs, nowadays, which are widely used for drug delivery vectors in animal models.<sup>171</sup> Compared with the drug delivery systems mentioned above, a notable property of CDs are their smaller size, which helps to penetrate the BBB and even the BBTB more rapidly and efficiently; thus allowing easier access to tumor cells for effective killing.<sup>172,173</sup> The size of the NPs is of particular concern to researchers because larger NPs may accumulate in important off-target tissues or organs, such as the spleen and liver, increasing their toxicity. Although, smaller NPs can be cleared more efficiently by the kidneys.<sup>173</sup> In addition, CDs can be organically modified and readily modified with tumor-targeting ligands and varieties of CT drugs, genes, or immune cells<sup>57,115</sup> leading to specific, receptor- or transporter-mediated targeted therapy with more efficient tumor cell uptake and lowered off-target effects, which are critical for the treatment of GBM. In future, the characterization and synthesis of CDs and the availability of selective treatment options will favor the practical application of CDs in clinical efforts against GBM.

## Abbreviations

BBB, Blood-brain barrier; BBTB, Blood–brain tumor barrier; CD, Carbon dots; EPR, Enhanced permeability and retention; NDDS, Nano drug delivery systems; OS, Overall survival; QD, Quantum dots; RCD, Red carbon dots; ROS, Reactive oxygen species; TfR, Transferrin receptors.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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